*The Journal of*
**NERVOUS and MENTAL DISEASE**

VOL. 130, NO. 5
May, 1960
SERIAL NO. 930

# AN ANALYSIS OF TYPES OF TREATMENT AND AN EXPLORATION OF ITS UTILITY

PHILIP LICHTENBERG, PH.D.,[1] RHONDDA K. CASSETTA, A.B.[1] AND JOHN C. SCANLON, D.S.S.[2]

## INTRODUCTION

This paper reports an examination of therapeutic practices in clinical settings with special attention to the actions and techniques of clinicians rather than to their theories. The long-range goal is to develop methods for describing mental health and disorder which will be useful in other, more community-centered, research. As a part of this larger effort, we have attempted to classify types of psychologically-directed treatment. This report contains an account of the system of classification so developed and the exploration of its utility in describing aspects of one hospital and factors associated with diagnosis and evaluations of severity of functional disability.

The system postulates two basic requirements. First, it must have internal organization, that is, the various parts must relate to each other in a prescribed way, through some general principle. Second, it must parallel and relate to something external, the continuum of mental health and disorder. The theory pertains to internal organization; testing the system pertains to its ties with mental disorder.

While there are many enumerations of various therapies in textbooks (*e.g.*, 12) and in reference works (*e.g.*, 1) or collections of therapists' viewpoints (*e.g.*, 7, 13), these listings fail to meet either of our two requirements. There have been some attempts to discover internal systems, usually by trying to abstract commonalities from diverse therapies. For instance, Fiedler (4), Black (2), and Strupp (10) have examined various therapies in search of the "salient features" common to them. Corsini and Rosenberg (3) reviewed some 300 articles in the literature and could organize these into nine general classes, three each within "Intellectual," "Emotional," and "Actional" types. In addition to our doubts about such an approach of abstracting from incomplete, unsystematic and inconsistently followed psychotherapies, we are not certain that these authors have organized the various therapies on unifying principles. Further, they do not seem to think it necessary to relate the variations in types of therapy to variations in patients, as in different severities of disorder. Szasz and Hollender (11) come nearest to our own requirements in examining models of the physician-patient relationship, but their interest in different means of sharing responsibility and the differences between medical practice and psychiatric practice preclude relations with diverse classes of treatment. In their analysis all psychological treatments fall in one model. Thus, we have discovered no existing analyses that fulfill our stipulated requirements, nor any solid comparative bases against which to examine our system.

## GENERAL CONSIDERATIONS

The unifying principle in our system may be called *mutual-achievement strivings*—a term coined because it emphasizes that all behavior, including that of a therapist, is

[1] New York State Mental Health Research Unit, Department of Mental Hygiene, 333 East Washington Street, Syracuse, New York.
[2] C. W. Post College, Long Island University, Greenvale, New York.

referred to the simultaneous integration of the alignment with other people and the alignment with the task. In *all* instances in our system the therapist is concerned with: 1) his alignment with the patient's intentions (his concern for mutuality); and 2) his orientation toward the goal of raising the mental health of the patient (his concern with achievement). Both these concerns for mutuality and achievement are comprehended in the term mutual-achievement strivings.

The therapeutic maneuvers in our system represent different levels of these mutual-achievement strivings. At the lowest level are minimums of mutuality (*e.g.* the patient is a social isolate) and of achievement (*e.g.* the patient cannot strive toward health in an adequate way). At the highest level, of course, the reverse is true. This formulation, therefore, defines treatments according to their positions on a continuum of mutual-achievement strivings. No treatment is preferable to another simply because it ranks higher on our continuum. Different maneuvers are relevant to different patients, and the appropriateness of maneuver to patient makes it "desirable" or not.

Because we cannot rate all of the possible interactions of the therapist with a patient, we have limited our consideration to: 1) those which are specifically intended to be "therapeutic," that are clearly expected to move the patient toward better mental health; and 2) those that comprise the dominant maneuvers, that occur with greatest frequency or are considered most strategic or decisive.

Since therapeutic maneuvers are defined in terms of the therapist's position vis-a-vis the patient's intentions, clarification of the word *intention* is appropriate. By a person's intention is meant the purposes or plans that the person consciously experiences with relative clarity of awareness. For example, a person who takes an overdose of drugs may intend to commit suicide or he may intend to control his wife by pretending to do so. To judge which alternate is true in any case, one must know the focus of the man's conscious experience. Intentions differ in the completeness and explicitness in which their future is specified. It is generally easier for others in the environment to mesh their own actions within spheres outlined by relatively incomplete intentions.

### THERAPEUTIC MANEUVERS AND TECHNIQUES

The system is based on four levels or degrees of mutual-achievement strivings. First presented is the maneuver with the greatest amount of mutual achievement; there follows consideration of maneuvers with decreasing amounts of mutual achievement.

The maneuver on the "highest" level maximizes both the mutuality and the achievement components. The therapist's actions affirm the expressed intentions of the patient as starting points for the development of new behaviors and ideas, while at the same time the therapist is revising and expanding the structure of the patient's intentions. The therapist is suggesting by his actions that the patient's intentions are *tentatively* acceptable, but acceptable only insofar as they are the origins from which will grow new intentions. The therapist aims to restructure or redefine the existing intentions, and in order to do this he starts with the intentions that exist. The therapist's alignment is within the general tenor of the patient's direction, but it is oriented toward lifting the patient from his current plane of intentional activity to a new one. The alignment of the therapist vis-a-vis the patient's intentions is shown in Figure 1, where it is designated Degree IV.

The next therapeutic maneuver aims less at the development of intentions within the treatment itself than at lending strength to those intentions of the patient that the therapist feels are relatively healthy. The therapist's actions in this case are essentially directed at affirming and fortifying these selected intentions. The therapist adds his weight to the direction of forces pro-

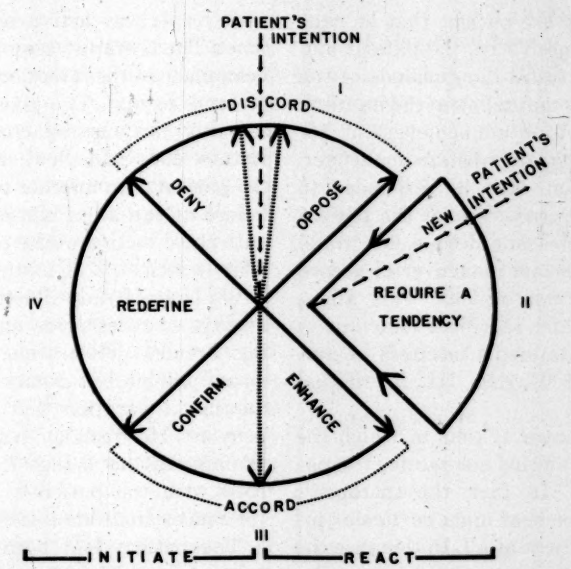


FIG. 1. Diagrammatic representation of therapeutic maneuvers and techniques with reference to mutual-achievement levels.

The line of short arrows going to the center of the large circle indicates as a direction toward a goal a patient's existing intention whether it was the basis for an interaction initiated by the patient or was activated by forces set in motion by the therapist. The large arrows indicate the direction of the forces brought to bear on the patient's intention by the therapist in the service of changing the mental health of the patient.

The small wedge set apart from the circle represents those situations in which the therapist is the protagonist trying to induce the patient to adopt intentions that are entirely new to the patient. In this instance the small arrows indicating the new intention formed by the patient emanate from the point at which the therapist's pressure is brought to bear. In all other cases the patient has had an intention prior to the specific interaction with the therapist.

There are four therapeutic maneuvers by mutual-achievement levels (redefine, accord, require a tendency, and discord) and six therapeutic techniques (redefine, confirm, enhance, require a tendency, oppose, and deny).

posed by the patient, so that his alignment is in accord with the patient's direction as shown in the figure. Indeed it is alignment of maximum accord. While there is maximum mutuality here between the patient and the therapist, however, this is not the same as maximum mutual-achievement strivings. The therapist's concern for mutuality is divorced to a certain extent from his goal of changing the patient's intentions in the interest of his improved mental health and is in some degree set off against that goal. Often enough, to be in accord with the patient's intentions is to invalidate efforts to change the patient's health. It is "being nice" to the patient. Freud (5) refers to the distinction between mutuality and mutual achievement, we think, in a neat passage in his discussion of "A Case of Obsessional Neurosis":

> "Here the patient broke off, got up from the sofa, and begged me to spare him the recital of the details. I assured him that I myself had no taste whatever for cruelty, and certainly had no desires to torment him, but that naturally I could not grant him something which was beyond my power. He might just as well ask me to give him the moon. The overcoming of resistances was a law of treatment, and on no consideration could it be dispensed with" (p. 304).

Thus, by telling the patient that he cannot both align himself with the patient and at the same time fulfill the demands of the task, Freud resists mutuality in the interests of a higher form of mutual achievement. He ends with our first therapeutic maneuver, that of redefinition. Had he responded to the patient with permission for the patient to avoid the unpleasant details, he would have taken this second maneuver of accord with the patient's intentions. This alignment of accord which sacrifices some immediate achievements in the interests of mutuality is called Degree III in mutual achievement.

The next maneuver is that in which the therapist neither affirms nor refutes the patient's intentions. In fact, the therapist's alignment does not bear upon *particular* intentions of the patient at all. In this case the therapist is attempting to introduce new intentions into the patient's behavioral repertory by inducing the patient to try new intentions and new actions. These new actions suggested by the therapist have no direct alignment with any of the intentions existing in the patient's life. Rather, the therapist acts to induce those behaviors and ideas that he thinks are likely to be satisfying to the patient and thus likely to be incorporated by the patient into his style of life. Since there is no direct connection between the actions suggested and the patient's intentional expressions, the therapist is drawing upon his understanding of what kinds of behavior are good for most people under most circumstances or those situations that are likely to surround the patient. This is Degree II in Figure 1 and is called "Require a Tendency." It is characterized by more emphasis upon achievement than upon mutuality.

Finally, there is a degree of mutual-achievement strivings in a therapeutic maneuver in which the therapist aligns himself in opposition to the patient's intentions. This action, of course, creates a minimum of mutuality between the patient and therapist with respect to active or probable intentions. The therapist aims to inhibit the development of the intentions that the patient presents to him. The given intentions, presumably, are unsatisfactory starting points for new ones, and the therapist must induce the patient into another plane of intentions before he can align himself more positively with the direction of the patient's activities. This is Degree I of mutual achievement.

We have already illustrated the two maneuvers of redefinition and accord in quoting Freud's deliberations with his obsessional patient, but it may be fruitful to give another illustration that contains two maneuvers. Hoedemaker (8) has written an example of the change from accord to discord with the patient's intentions. A few references from his article are illuminating.

The patient had been following a pattern of first drinking excessively and then demanding that the doctor give her quieting drugs. She would ask for sedatives because she feared she would be unable to sleep, or would have a convulsion, or would "fly to pieces." The doctors and nurses, reacting to the implicit threat in her behavior, conformed to her intentions by giving her the drugs. This sequence would then be repeated. Hoedemaker claims that a new ego structure was established by shifting his position. Partly from annoyance, about which he was uneasy, and partly from insight, he instructed the nurse to tell the patient that he would not allow her to have sedation. Since this was in the midst of the patient's demand for such sedation, the nurse was somewhat resistant, but Hoedemaker insisted on his instructions being carried out. He had chosen to deny the intention instead of confirming it. At the same time he pointed out that the nurse was also to tell the patient she could be as afraid of convulsions, etc. as she needed to be. The patient reacted immediately with anxiety and misgivings, but quieted down shortly thereafter. A few more episodes identical to this followed, but with decreasing intensity.

Subsequent to those episodes the patient took no sedatives nor did she drink heavily for some fourteen months, though nothing directly pertaining to these considerations entered the therapy during that time. Hoedemaker's change from accord to discord with the patient's intention apparently signaled a radical change in the patient's life.

These four therapeutic maneuvers are represented in our study by six therapeutic techniques, presented in Table 1. The development of six techniques from four levels of mutual-achievement strivings is required by the fact that Degree IV (redefinition) is asymmetrical with Degree II (require a tendency) on a basic issue. In order that he may redefine, the therapist must *react* to the patient; in order that he may try to introduce an entirely new intention, he must *initiate* goals and actions. Heider (6) touches upon this issue when he speaks of attribution:

> "For instance, our subjective environment contains the self and another person and a new event occurs: one of the persons will be held responsible for it."

What is meant here, we think, is the specification of who initiates the issue that comes to be the focal point of the transaction. Our interest, in contrast to Heider, is not with the patient's attribution of responsibility; we wish to make some objective account of who plays the dominant role in establishing the major issue that characterizes the transaction.

Although redefinition (Degree IV) can exist only when the therapist is reactive, and requiring new intentions (Degree II) can exist only when the therapist takes the initiative, the other therapeutic maneuvers are not restricted in the same way. The therapist can place himself in accord with the patient (Degree III) both when he is reactive and when he takes the initiative. When he reacts, he can *confirm* the intentions presented to him; when he assumes the initiative, he can *enhance* tendencies that already exist in the patient's current intentional life. Similarly, the therapist can be in discord with the patient (Degree I) by reactively *denying* the given intentions or initiating an *opposing* orientation to existing tendencies. Thus, the four levels of mutual-achievement strivings fan out into six techniques, one each for maneuvers IV and II and two each for maneuvers III and I. It is these six techniques which appear in most conventional descriptions of therapies.

TABLE 1

*Outline of Types of Treatment by Therapeutic Maneuver*

| Therapeutic Maneuver | Techniques of Therapy |
|---|---|
| Degree IV—Redefine | 1. Uncover and interpret intentions |
| Degree III—Accord | 2. Confirm—*support* intentions<br>or<br>3. Enhance—*change situations* to provide outlets for intentions |
| Degree II—New Intentions | 4. *Direct* patient to try new intentions |
| Degree I—Discord | 5. Deny—*protect patient* against intentions (including drugs and shock treatment)<br>or<br>6. Oppose—*protect others* against intentions by controlling patient |

### THEORETICAL RELATION OF TREATMENT TO CHARACTERISTICS OF THE PATIENT

The differing degrees of mutual-achievement strivings described are associated with the number and complexity of the intentions with which the patient-therapist relation deals. That is, when the therapist aims to redefine, he attempts to bring into the task a maximum number of intentions in the patient's life, and the most complex ones. When the therapeutic maneuver is that of discord with the patient's intentions, the therapist is directing his treatment efforts

to the few or simplest or most basic intentions.

The process of redefining implies a direct operation upon and rearrangement of the intentional life of the person. Such direct modification necessitates the availability to the treatment process of most needs and intentions. The strict rule of psychoanalysis to the point that the patient must relate everything that comes to mind is an embodiment of this implication.

The process of the therapist placing himself in accord with the patient involves fewer intentions than when the therapist is restructuring. This is equivalent to saying that some achievement is sacrificed for the development of mutuality between patient and therapist. The therapist cannot accord with or support the maximum number of the patient's intentions because he does not wish to foster in his treatment setting the appearance and development of self-defeating intentions. Were these self-defeating intentions to be confirmed, the therapist would be encouraging illness, not health, and would depart from his goal.

When the therapist requires entirely new intentions in the third maneuver, he is forced to deal with an even more restricted range of intentions. The therapist's aim is to enlarge the patient's repertory of intentions by introducing new ones for the patient to adopt exactly as presented. Two sets of limitations restrict the range of intentions available to the therapist in this maneuver: 1) he must require intentions that the patient has not formulated for himself at some prior time; and 2) he cannot require intentions that are too alien to the patient (since this would place the therapist in immediate discord) or are too similar to other intentions of the patient (for this would place the therapist in immediate accord).

Finally, when the therapist sets himself in discord with the active intentions of the patient, he is devoting his efforts to a very few of the patient's intentions. If he tries to deny or oppose many intentions, he will be keeping the patient from any action, and this is not psychological treatment. The therapist can afford to align himself in discord with only a few, strategic intentions if the relationship is to continue, and these are usually without major complexity.

The differing degrees of mutual-achievement strivings are associated with the amount of the patient's life that must be geared to the therapeutic endeavor as well as to the number and complexity of intentions that are dealt with. There is an inverse relation between these factors: the fewer the intentions with which the therapist is to concern himself, the more of the patient's life it is necessary to have available for *possible* therapeutic intervention. This is the case because the therapist must be more selective in regard to the intentions he aligns himself with. As we have pointed out above, for instance, when the therapist puts himself in discord with the patient, he must choose strategic intentions for his treatment activities. The particular choice among all intentions is more important in direct proportion to the number of intentions that will fall within treatment. To know which intention should be chosen it is valuable to have a maximum of information, and this requires much contact with the patient's life. Similarly, to act in reference to a specific intention, the patient and the therapist must be reasonably available to each other, and this is best accomplished when the therapist is associated generally, but not always therapeutically, with the patient's living conditions. Thus, both for the needed information on which to base a decision and for circumstances that facilitate the implementation of decisions, the therapist must have more extra-therapeutic contact with the patient to the extent he goes from a redefining maneuver to one of discord with the patient's intentions.

## METHOD AND RELIABILITY

This system, with the six techniques of treatment supplemented by the three cate-

gories of "no treatment," "not established," and "other," was included in a clinical record form relevant to disposition case conferences. Thus, the conventional descriptions of therapies could be recorded, to be later integrated in terms of levels of mutual-achievement strivings. This rating schedule, which also incorporates items on functional disability and diagnosis, was filled out by the writers when these patients and their histories were presented by the responsible residents and interns to the director of the hospital or to the assistant director. The written records about these patients kept by the hospital were also checked in the search for relevant information. Near the end of the presentation and analysis of each case it was customary for the director to lead a discussion on the treatment that should be given to the patient. From these discussions a general point of view usually emerged, which was then translated into one of the categories in this system. It should be noted that persons other than research team members made the decisions that were recorded. Their biases are far from the positions we take, so that relations found in statistical comparisons are unlikely to be spurious on this account.

A few notes made at the conferences pertinent to different decisions may help to illustrate our procedures as well as the content to which the categories refer. With respect to a patient for whom we judged an *uncovering* (*i.e.* redefine, see Table 1) treatment was being prescribed, our notes read:

> "Because she can talk directly about her problems, she can be a good candidate for therapy ... My [the presenting resident] approach has been to point out her feelings ... Often patients like this can be treated as outpatients ... These people support analysts ... Work very actively with these people ... Attempt to establish a baseline of facts ... Be warm and friendly, but do not be too kind."

About two patients for whom *supportive* care (one technique of accord) is prescribed these remarks appear in our notes:

> "Take the tactic of what does it mean for her ... Steer clear of explorations ... Keep on drugs ... Allow catharsis ... Reassure her ... She is suggestible ... Use suggestion with the transference."
>
> "Hospital is a place of refuge ... Husband has agreed to look for new place she desires ... Get feeling you can work with this girl ... Nobody has given her support ... I [the presenting resident] have tried to sustain her ... Enhance her ego level ... I have much experience with her type of problem; she needs a lot of support ... Can be built up ... Amenable to suggestion, guidance."

We labeled the therapeutic technique applied to the next patient *directive*:

> "Keep her here and see if she remits ... Help her reorganize her life ... Send her to a hairdresser, get her to look better in her clothing and appearance."

Finally, two patients were given more stringent forms of therapy, which belong in the lowest level of mutual achievement, discord:

> "Give her shock treatment to control her ... The alternative is the large state hospital ... See her briefly a couple of times a week."
>
> "Wants to stay on third floor [closed ward] ... Let him feel he is being contained, held in ... He would not profit from an open hospital ... If no response in two or three weeks, send him for long-term care."

It was common in these discussions of techniques that a gradual settling upon a decision followed upon an exploration of the relevant alternatives. Not all comments, thus, refer to the finally chosen types of treatment.

Two members of our research group independently filled out a rating schedule on each patient presented. Thus, all recordings were made by one of the three teams of two members each from our research group of three people. Team 1 recorded 60 cases; Team 2, 58 cases; and Team 3, 19 cases.

After each case conference all three members of the research group (the team that had recorded the case plus the remaining researcher) met and discussed the ratings

made independently by the two team members and the information on which the ratings had been based. The final rating of the patient was established by the consensus of the three members of the group (two of whom had actually seen the patient) after consideration of the individual ratings and the relevant data presented. Finally we reread each patient's case folder and discussed any additional material that bore upon our ratings, making any adjustments we felt warranted.

To check the reliability of raters' observations of the technique presented as desirable for the particular patient at his case conference, we compared the ratings made by the team members. There was full agreement regarding techniques chosen by Team 1 in 75.0 per cent of the cases they reported; by Team 2, in 70.7 per cent; and by Team 3, in 63.2 per cent. Thus, there was full agreement in type of treatment rated in 69.6 per cent of all cases, excluding from the reliability evaluation the first 25 cases that were used for training purposes.

When the ratings are examined on the basis of the four maneuvers, the percentages of full agreement of raters increase slightly to 78.3 per cent for Team 1; 74.1 per cent for Team 2; but remained at 63.2 per cent for Team 3. It is likely that the small number of cases rated by Team 3 (only 19) is a factor in lowering its level of full-agreement as compared with the other two pairs of raters.

For the 30 per cent of the cases where disagreement in ratings was present, no pattern of consistent bias emerged on the part of a single observer, indicating that the observers were responding to the issues raised in the study's setting, rather than that the form favored a particular observational orientation or channeled observations selectively.

## APPLICATIONS OF THIS SYSTEM

A system that organizes types of treatment is relevant to the following interests:

1) It enables one to characterize a clinical setting. For example, hospital A dispenses treatment X predominantly, while it seldom dispenses treatment Y.

2) It enables one to contrast clinical settings. For example, hospital A dispenses treatment X predominantly, while hospital B dispenses treatment Y predominantly.

3) It enables one to compare a clinical setting with other settings. For example, hospital A dispenses treatment X precisely to those patients whose non-hospital life is characterized by participation in groups where alignments and goals are similar to treatment X.

4) It enables one to explore the relations between personal characteristics of the patient and the type of treatment he is given. For example, patients with diagnosis N are given treatment X predominantly.

In this report only the first and last of these above issues are investigated. It can be seen that the values of the system in these two areas must be demonstrated before it is worthwhile to pursue the others. If the system does not characterize a single institution, it would be unwise to use it to contrast separate settings.

## A PRELIMINARY DESCRIPTION OF SYRACUSE PSYCHIATRIC HOSPITAL

The system of therapeutic maneuvers and techniques was applied to 164 patients admitted to Syracuse Psychiatric Hospital[3] between late October, 1958 and early June, 1959. These cases represent about seventy-five per cent of all patients admitted to this hospital during that period and are a fair sampling of the total, with the exception that patients sent by the courts for "observation" are excluded. Syracuse Psychiatric Hospital is a 60-bed state hospital that is oriented toward diagnosis and short-term treatment. It is connected with the State University of New York, Upstate Medical

[3] Dr. Marc Hollender, Director of the Syracuse Psychiatric Hospital, was most helpful in encouraging us to work within his setting.

Center, as a teaching and research hospital. Almost all types of patients are admitted and a wide variety of types of treatment are prescribed and administered. By diagnostic classes, according to our analysis with the APA Diagnostic and Statistical Manual of Mental Disorders, 1952, revised, the sample making up the study group is constituted as noted in the first column of Table 2.

At the disposition case conferences the research group recorded an estimate of the therapeutic technique thought to be most desirable or ideal by the staff, and that actually suggested by them. Since we found little difference between desirable and suggested techniques (15 cases; 9 per cent of the sample), we present information on the desirable techniques only. This material is summarized in Table 2.

It is clear, first, that all techniques are considered pertinent, a fact that accords with the diversity of patients admitted and the range of treatments needed for good teaching and research purposes. Second, it may be noted that the heaviest loading of cases is in the maneuver with least mutual-achievement strivings (Degree IV). The greater extra-therapeutic contact with the patient that follows from hospitalization is needed for this level of mutual-achievement strivings, as we noted earlier. Thirdly, directive treatment, in which the therapist tries to introduce new intentions directly, is underplayed in this hospital. This technique would probably include strong occupational therapy and milieu therapy programs. In this setting these programs were being developed at the time of our study but were not adequate at that time.

Finally, those treatments in which the therapist is reactive are more often prescribed than those in which he takes the initiative. A small part of this difference is due to the weak state of directive treatment, as noted above. Thus, uncovering treatment is given to 22 patients while directive treatment is given to only ten. But the react-initiate distinction carries throughout. Within Degree III (Accord) the therapist reacts by confirming in 24 cases and initiates by enhancing in only 15. Similarly in

TABLE 2

*Number of Patients Within Diagnostic Classes and Desirable Treatments*

| Diagnostic Class | n | Treatments | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Degree IV Uncover | Degree III | | Degree II Direct | Degree I | | No Treatment Not Established or Other |
| | | | Confirm | Enhance | | Deny | Oppose | |
| Schizophrenia | 44 | 0 | 5 | 2 | 6 | 13 | 17 | 1 |
| Affective Psychoses and Involutional Melancholia | 27 | 0 | 3 | 0 | 1 | 22 | 0 | 1 |
| Personality Pattern or Trait Disturbance, Paranoid Reaction | 9 | 1 | 0 | 2 | 0 | 1 | 2 | 3 |
| Sociopathic Personality Disturbance | 13 | 2 | 2 | 3 | 1 | 2 | 1 | 2 |
| Psychoneurotic Reactive Depression | 26 | 9 | 11 | 2 | 0 | 2 | 0 | 2 |
| All Neuroses Other Than Depression | 15 | 8 | 3 | 2 | 0 | 0 | 0 | 2 |
| Transient Situational Personality Disorders | 10 | 2 | 0 | 3 | 0 | 0 | 0 | 5 |
| Acute and Chronic Brain Disorders | 11 | 0 | 0 | 0 | 0 | 3 | 2 | 6 |
| Other Diagnoses | 9 | 0 | 0 | 1 | 2 | 5 | 1 | 0 |
| Totals | 164 | 22 | 24 | 15 | 10 | 48 | 23 | 22 |
| | | | 39 | | | 71 | | |

Degree I (Discord) the therapist tries a denying technique in 48 cases (only 16 of which are electric shock therapies) and an opposing technique in but 23 cases. If all techniques in which the therapist reacts are combined and compared with all in which he initiates, the ratio is almost two to one (94/48). This ratio seems lopsided in favor of the reactive maneuvers, a fact that is consistent with the general psychoanalytic orientation of the hospital.

## CHARACTERISTICS OF PATIENTS

### DIAGNOSIS

The major findings that are associated with diagnosis in relation to therapeutic techniques are also summarized in Table 2. The first observation to be made is that psychotic patients (persons diagnosed as schizophrenics, affective psychotics or involutional melancholics) tend to be given Degree I treatments; and those diagnosed as neurotics tend to be given Degree IV or III treatments. The distributions in other diagnostic classes approximate the relations of the classes to psychosis and neurosis. Those classes nearer psychosis (*e.g.* Personality Pattern Disturbance) have proportionately more Degree I treatments, while those nearer neurosis (*e.g.* Transient Situational Personality Disorders) have more Degree IV and III treatments.

The next consideration involves the specificity of a type of treatment with respect to a given diagnosis. There is one area of marked specificity as shown in the table. For patients diagnosed as being within the affective psychoses or involutional melancholia, the major technique, given to 81 per cent of these people, involves protecting the patient against his impulses. In essence the therapist allows the patient to do what he wants up to the point where specific impulses begin to overwhelm him, whereupon the therapist reactively intervenes to help protect the patient against these impulses.

Within the diagnosis of schizophrenia there are two modal techniques, *deny* and *oppose*, both falling within Degree I. The question persists in our minds whether a single technique (oppose) is truly more relevant to schizophrenia; but partly because it is less well understood and partly because it requires therapist initiative and assumption of responsibility, it is not consistently applied. We have touched upon the latter observation in noting that Syracuse Psychiatric Hospital emphasizes techniques in which the therapist is reactive. The other point may be mentioned if not developed. Our shorthand description of this technique is "to protect others from the patient's probable intentions, impulses, and ideas by controlling the patient." Such a technique can be therapeutic only insofar as there is a mutuality in achievement. This can occur only if the protection of others through control of the patient involves two *explicit* elements: 1) the protection of others is at the same time beneficial to the patient; and 2) neither the patient nor the other suffers greater harm than his counterpart in the process. If we take the therapist himself as the "other" in the case, the treatment intervention would be something like this: "I will not permit you to harm or exploit me such that I would have need or cause on that account to harm or exploit you. Rather, I will inhibit your exploitative maneuver and thereby inhibit any chance that I might harm you." In this connection we have seen therapists threaten to send patients to a place where more strict control over the patient would be applied. This was done straightforwardly, rationally, and without guilt (all of which are necessary) with no harmful intentions but with practical necessities—and the patients have responded positively. Again there was mutuality in the task and the "villain" was the structure of the setting in which the patient's harmful behavior could not be tolerated.

Psychoneurotic patients were also given two techniques (uncover—interpret and support) but these are in Degrees IV and III respectively. Within this class a further analysis is useful. In this group of patients,

twenty-six were diagnosed as reactive depressions and fifteen were diagnosed in the other neurotic categories (mainly dissociative and conversion with some anxiety and phobic reactions). Within reactive depressions, nine persons were given uncovering treatment and eleven were given supportive care. Thus, there are two alternatives of almost equal frequency. Within the other neurotic patient group, however, eight of the fifteen were given uncovering treatment and no other type was given to more than three people. Thus, these other neuroses were most likely to be given uncovering treatment. Otherwise, they received no treatment, supportive treatment or enhancing manipulations of their environments, all of which emphasize the *status quo*.

One further set of observations, relevant in this section, concerns the react-initiate issue. This matter can be studied by combining the uncovering, confirming and denying techniques and comparing them with the combined enhancing, directing and opposing ones. The affective psychoses and all psychoneuroses are associated with techniques in which the therapist is reactive and the patient assumes major responsibility for that which enters the treatment. The react-initiate ratio by patients is 25:1 for the affective psychoses and 33:4 for the neuroses. A reverse tendency is found for schizophrenic patients and those in the combined class of Personality Pattern or Trait Disturbance and Paranoid Reactions. (This class is dominated by the diagnoses of Schizoid Personality, Paranoid Personality and Paranoid State.) The ratio of schizophrenics is 18:25 and for the combined class 2:4. The remaining diagnostic classes do not show tendencies in either direction on this variable.

### SEVERITY OF FUNCTIONAL DISABILITY

The data regarding diagnoses and therapeutic techniques tend to support our expectation that the system of maneuvers and techniques would be associated with severity of disturbance. We have also examined the relation of therapeutic maneuvers to a direct estimate of severity of mental illness which we call functional disability. An extended description of this analysis will be presented elsewhere, but a brief one follows.

With respect to functional disability, we distinguish between four foci of relations: 1) self-others; 2) self-things; 3) self-body; and 4) self-psyche. It is apparent that in all behaviors all four of these regions are relevant, but they are not always the center of attention (*i.e.* figural) in the patient's life. Thus, the patient's intentions may be directed toward resolving his relations with other people, but obviously his body, his feeling state and his relations to things enter into these interpersonal activities. On the basis of clinical data available, we estimate the proportion of all possible behaviors in any of these regions that are likely to be disrupted by psychological conflict. From this estimate, we have in effect the range of probable behaviors available to each person. Healthy people tend to have more probable behaviors available in all areas of focus. Adding the extent of disability in each of the four focal areas provides an estimate of the degree to which a person's total life is restricted. Thus, a composite measure of functional disabilities yields a general idea of the degree of mental illness.

From all disabilities and conflicts made public by the patient, his family or hospital personnel and noted in case conferences or in a patient's records, the research team rated each of the four areas on the functional disabilities in that area. A four-point scale, consisting of ratings of *no disability, mild, moderate or severe disability*, yielded a score for each area from 0 to 3. Summing the four areas of self-others, self-things, self-body, and self-psyche permits a range on the composite scale from a score of 0 to a score of 12. For the 164 cases reported, the spread of observed severities is from 1.5 to 11.0 with a mean of 5.6, a median of 5.5 and a standard deviation of 1.6. The correlation coefficients of agreement between

TABLE 3

*Rank of Functional Disability by Treatment Desirable*

| | Treatments | | | | | |
|---|---|---|---|---|---|---|
| | Degree IV Uncover | Degree III Confirm-Enhanc | Degree II Direct | Degree I Deny-Oppose | No Treatment | Other or Not Established |
| Number Cases | 22 | 39 | 10 | 71 | 13 | 9 |
| Sum Ranks | 710.0 | 2426.5 | 1030.0 | 8389.0 | 602.5 | 372.0 |
| Median Rank | 30.3 | 54.5 | 102.5 | 122.0 | 32.0 | 26.0 |
| | | | $H = 87.92^*$ | | | |
| | | | $p < 0.001$ | | | |

* Kruskal-Wallis H-Test

TABLE 4

*Significance of Differences Between Mean Functional Disability Scores and Treatments*

| Treatment | n | Mean Score | Variance | Significance |
|---|---|---|---|---|
| Degree I & II | 81 | 6.7 | 1.75 | 0.0001 |
| Degree III | 39 | 5.0 | 0.82 | 0.0001 |
| Degree IV | 22 | 4.1 | 0.72 | |

independent raters are 0.76, 0.74 and 0.47, the lowest figure referring to the pair of raters who had the fewest cases.

The first check in this area involves the whole sample and applies the Kruskal-Wallis H-test (9). The 164 cases are ranked according to functional disability scores. Then the sums of ranks within the treatment categories are compared. We expect that there will be a parallel between degree of mutual achievement and of functional disability. The material is presented in Table 3, and it confirms the thesis under scrutiny by rejecting the null hypothesis.

A comparison of means was also done by the usual t-test. In order that normality be approximated it was necessary to combine Degree I and II. The results of this analysis appear in Table 4; they add confirmatory evidence to the relation of severity and therapeutic technique.

It will be clear to the sophisticated reader (but must be made explicit in any case)

TABLE 5

*Significance of Differences in Numbers of Patients Below Median and at or above Median in Each of Three Diagnostic Classes by Level of Treatment Desirable*

| | | Degree of treatment | | | | | |
|---|---|---|---|---|---|---|---|
| Functional disability | Range | None or not established | IV | III | I + II | Total | Probabilities[3] |
| **Schizophrenia** | | | | | | | |
| Low[1] | 5.0–6.2 | (1) | — | 7 | 13 | 20 | 0.002 |
| High[2] | 6.5–9.5 | — | — | 0 | 23 | 23 | |
| Total | | | — | 7 | 36 | 43 | |
| **Affective psychoses and reactive depression** | | | | | | | |
| Low[1] | 3.2–5.3 | (2) | 8 | 11 | 4 | 23 | |
| High[2] | 5.5–7.7 | (1) | 1 | 5 | 21 | 27 | <0.001 |
| Total | | | 9 | 16 | 25 | 50 | |
| **Psychoneuroses (except reactive depression) and transient situational personality reactions** | | | | | | | |
| Low[1] | 2.3–3.5 | 5 | 5 | 1 | — | 11 | |
| High[2] | 3.7–6.0 | 2 | 5 | 7 | — | 14 | $0.05 < p < 0.10$ |
| Total | | 7 | 10 | 8 | — | 25 | |

[1] Below median

[2] At or above median

[3] The exact test was used for schizophrenia; for affective psychoses and reactive depression, 2 d. f., $\chi^2 = 19.13$; for other neuroses and situational, 2 d. f., $\chi^2 = 5.41$. It must be noted, however, that the theoretical frequencies used in the $\chi^2$ analysis are borderline, especially with reference to the psychoneuroses comparison.

that there is considerable overlap in the classes of treatment with respect to severity of functional disability. For example, persons with functional disability scores slightly below the mean (5.0–5.5) are found in every treatment category in the analysis. About one-fifth of all the cases (35/164) are found within this range, so that there is little specificity for a sizable portion of the total group. Thus, while the mean scores show significant differences, the specificity of relation between therapeutic maneuver and severity of illness is not precise.

### DIAGNOSIS AND SEVERITY OF FUNCTIONAL DISABILITY TAKEN TOGETHER

Since diagnosis and functional disability as independent estimates of mental illness relate to therapeutic maneuvers, they may show a stronger relation when taken together to form a joint estimate of severity. Our analytic procedure follows. Three diagnostic groupings have been used: 1) all schizophrenic patients; 2) all patients with depression as the dominant theme—affective psychoses, involutional melancholias and psychoneurotic depression reactions; and 3) all patients with neuroses other than depression (dissociation, conversion, phobic, anxiety) and all transient situational personality disorders. Within these diagnostic groupings the relation between therapeutic maneuver and severity of functional disability is explored. The results are presented in Table 5.

The findings, which cover about three-fourths of all persons studied, reveal the superiority of having specifications in both diagnosis and severity of disability when choice of treatment is under consideration. Within each of the three diagnostic groupings the lower functional disability scores are associated with higher degrees of mutual achievement in treatment.


### SUMMARY

In this paper an attempt has been made to present a classification of therapeutic maneuvers and techniques according to degrees of mutual-achievement strivings. In a theoretical formulation we have tried to portray its internal, systematic properties. We have also brought data to bear upon our supposition that the system, by which we have organized therapeutic maneuvers and techniques, is related to severity of mental disorder and, in some respects, to various qualities of mental disorder as these are reflected in diagnosis.


### REFERENCES


1. *American Handbook of Psychiatry,* Arieti, S. ed. Basic Books, New York, 1959.
2. Black, J. D. Common factors of the patient-therapist relationship in diverse psychotherapies. J. Clin. Psychol., **8**: 302–306, 1952.
3. Corsini, R. J. and Rosenberg, B. Mechanisms of group psychotherapy: Processes and dynamics. J. Abnorm. & Social Psychol., **51**: 406–411, 1955.
4. Fiedler, F. E. A comparison of the therapeutic relationships in psychoanalytic, non-directive and Adlerian therapy. J. Consult. Psychol., **14**: 436–445, 1950.
5. Freud, S. Notes upon a case of obsessional neurosis. In *Collected Papers,* Vol. 3, pp. 296–383. Hogarth Press, London, 1953.
6. Heider, F. *The Psychology of Interpersonal Relations.* Wiley, New York, 1958.
7. Hoch, P., ed. *Failures in Psychiatric Treatment.* Grune & Stratton, New York, 1948.
8. Hoedemaker, E. D. Preanalytic preparation for the therapeutic process in schizophrenia. Psychiatry, **21**: 285–291, 1958.
9. Kruskal, W. H. and Wallis, W. A. Use of ranks in one-criterion variance analysis. J. Am. Statistical A., **47**: 583–621, 1952.
10. Strupp, H. H. A multidimensional system for analyzing psychotherapeutic techniques. Psychiatry, **20**: 293–306, 1957.
11. Szasz, T. S. and Hollender, M. H. A contribution to the philosophy of medicine: The basic models of the doctor-patient relationship. A.M.A. Arch. Int. Med., **97**: 585–592, 1956.
12. Thorpe, L. P. and Katz, B. *The Psychology of Abnormal Behavior.* Ronald, New York, 1948.
13. Wortis, S. B., Herman, M. and Hare, C. C., eds. *Psychiatric Treatment.* Williams & Wilkins, Baltimore, 1953.

# PSYCHOLOGICAL STUDIES OF KORSAKOFF'S PSYCHOSIS: VI. MEMORY AND LEARNING[1]

GEORGE A. TALLAND, PH.D.[2]

Korsakoff's psychosis provides the perfect example of a disease which can conveniently be described by one salient symptom: the amnesic syndrome. Patients in the chronic phase of this disease display a memory defect out of proportion in its severity to any other symptoms they may have. This disorder is manifested alike in a failure of deliberate recall and a virtual incapacity to learn, *i.e.*, to acquire new skills, habits or knowledge. But for the fact that their amnesia tends to be retroactive, it would appear that the disturbance is one of registering new impressions. The memory defect does usually extend to periods of varying length prior to the onset of the disease, however, and the amnesia is not absolute even for events which have occurred since that time. Reports in the literature iterate the observation that Korsakoff patients do retain some impressions which they are able to recognize or to reproduce, though haphazardly rather than at will; many of them also learn entirely new skills, *e.g.*, finding their way about the hospital.

An attempt to explain the memory disorder in the amnesic syndrome may imply nothing short of a complete theory of remembering, and that in turn is likely to form part of a more general theory of cognitive processes. While observations made on Korsakoff patients should make valuable contributions towards the formulation of such a general theory, as yet none has been constructed that could satisfactorily account for these abnormalities, and any explanation advanced in conjunction with clinical or experimental findings is of necessity tentative, and, perhaps, only of heuristic significance. In previous reports (21–24, 26) the case was stated that the cognitive disturbance in Korsakoff's psychosis extends beyond memory functions, and an attempt was made to suggest possible functional relationships as well as parallels between defects in perception, concept formation and memory disturbances in Korsakoff's psychosis. The purpose of this report is to present several findings concerning the memory functions and learning capacities of Korsakoff patients, based in part on interview material and in part on experimental procedures. In discussing these, an attempt will be made to fit the observations on the Korsakoff syndrome within a theoretical model.

## SUBJECTS

The patients who will be discussed were all in the chronic phase of Korsakoff's disease, eight men and 16 women who had spent periods from one to several years at the Boston State Hospital. They all had a history of alcoholism prior to their hospitalization, initially for Wernicke's encephalopathy, and had almost entirely recovered from the neurological symptoms of that disease. Their social background was in most instances that of the Boston working and lower middle classes of Irish extraction; their IQ, estimated from three subtests (CVS) of the Wechsler Bellevue Scale, was in the average range (mean = 103.4, SD = 8.9); their ages at the beginning of the research varied between 31 and 74 years

[1] This work was supported in part by a Research Grant M-767 from the National Institutes of Health.

[2] Department of Neurology and Neuropathology, Harvard Medical School; Department of Psychiatry and the Neurology Service, Massachusetts General Hospital, Fruit Street, Boston. Psychology Laboratory, Department of Psychiatry, supported in part by Air Force contract AF-49-(638)-98: The Merrill Trust; The Harrington Trust, Harvard Medical School.

(mean = 53.3, SD = 9.3). In most of the experimental procedures their performance was tested against one or two control groups matched for age; the one, with a history of alcoholism but functioning reasonably well in society and without any alcohol in their system, the other, neurological patients with a history of prolonged hospitalization at the time of testing, but without records of alcoholism or of brain damage other than characteristic of the normal aging process. Further details of the several groups of subjects and of the experimental conditions were given in earlier reports of this series (22, 27).

### INTERVIEWS

The general impression created by the Korsakoff patients conformed to the picture presented with considerable uniformity in the literature. They were rather listless but cooperative, rarely initiating conversation but always ready to respond. Their answers tended to be short and factual, hardly ever straying far beyond the question raised, or into any vagaries of 'confabulation.' As a rule their talk was even-tempered, and not infrequently spiced with a joke. They could, of course, say more about events or their lives prior to hospitalization than in the recent past, but there was considerable variability among the patients in this respect. Some were quite well oriented about their routine activities in the State Hospital, and all seemed to know their way about there; several also learned the somewhat labyrinthine path from the entrance of the Massachusetts General Hospital to the psychological laboratory, after a few visits. A few patients were utterly vague when asked how they spent their days, but they had little enough to report. A number of the patients also showed noticeable improvement in their familiarity with their surroundings and daily routine as the years went by, an improvement which could not be detected with certainty by formal tests of memory or learning. All those studied had retained such old skills and habits as are used in dressing, eating, and polite conversation, and none had any noticeable loss of vocabulary.

A series of standardized interviews was conducted with 18 patients at about the end of the second year of the investigation, when each of them had met the experimenter on at least twenty occasions, either at the Boston State Hospital or in the experimental laboratory at the Massachusetts General Hospital. All of these patients recognized or thought they recognized him and identified his role in relation to themselves with reasonable accuracy. Two or three confused him with other doctors, and thus attributed to him medical examinations or the administration of procedures for which he was not responsible. Seven patients recalled his name correctly, three came near to it on first trial, two others could remember it five minutes after being told, six failed entirely. When asked where they had seen him before, they all answered that it was in the same place, and all but three were able to name it as the Massachusetts General Hospital. The other three thought the interview was taking place at the Boston State Hospital which every one of the 18 patients knew by its proper name or some reasonable approximation, *e.g.* Mattapan State Hospital, or Massachusetts State Hospital; several of them also volunteered its address. However, on being asked whether they had met the interviewer at any other place, only six answered affirmatively, and any significance of the three correct responses is offset by the other three which came from the very same patients who had mistaken the site of the interview.

The patients were asked to state on two occasions when they had last seen the interviewer, once after the actual lapse of at least four months since their last encounter, a second time after an interval of one to two weeks. Following the longer period, 15 patients thought they had been at the laboratory within the past month, one assessed the interval accurately, two suggested it must have been a year or so, indicating rather vaguely that it was a long time ago,

longer in fact than it actually was. The estimate of the short term was typically "last week" or "a month ago, or less"; though in a few instances it was an indefinite "not so long ago," and the interviewer had to find out whether this meant a week, a month, or longer. All the 15 patients who underestimated the long time interval and a sixteenth who assessed it correctly, gave a more or less accurate answer when they returned within a week or two; the remaining two, however, persisted in thinking that about a year had elapsed since their last visit, thus confirming Williams and Zangwill's (30) observation about a tendency to antedate recent events.

Asked how many times they had previously been at the place of the interview, three patients overestimated the number of occasions, one of them clearly confusing the experimenter with a doctor whom she remembered as having examined her weekly for a period of over a year. Nine patients were under the impression that they had been at the place two, three or four times before, eight thought that this had happened once only. In fact, they had been at the laboratory some 12 to 15 times prior to the interview.

The occasion of the interview followed shortly after the Presidential election in the U.S.A. and two memorable events farther afield which, however, were given considerable publicity at the time in Boston. One was the ill-fated Hungarian revolution of October–November, 1956, the other the abortive Franco-British expedition to the Suez Canal. The patients were asked if they knew anything about these events, each being mentioned in turn. Their typical response was evasive, mentioning lack of opportunity to read papers or the temporary breakdown of the television set at the hospital. Nevertheless, every one knew Eisenhower's name and brought it up in connection with the first question, though two patients would not credit him with the victory he had just won. They demonstrated the sequential confusion of events so typical of Korsakoff psychosis, in believing that the President just elected was Roosevelt or Truman, though Eisenhower too had been elected on a previous occasion. The other names prominent in that election campaign were virtually unknown to the patients, and were mentioned less frequently than those of several local politicians as well as the two ex-Presidents. Only one patient recalled the names of both principal contestants for the office, and that remarkably enough was a woman (H.T.) who on many other occasions provided the most extreme instances of amnesia, *e.g.*, a complete inability to recall after two or three minutes the name of the experimenter or of a colleague of hers, or practically anything she had heard, read, or seen.

Two patients were fairly well informed about recent events in Hungary and in Suez; three others gave answers which may have been based on actual information, but may have come from any other source in their generality, *e.g.* "disaster," "perhaps revolution," "starvation," in Hungary. The last of these, though patently inaccurate, may nevertheless have been founded on some factual report, for the patient elaborated her report that "the Hungarian people are starving to death" with "they cannot get them any food by air or sea, because of the war." She also reported that in Suez "a ship blew up a few weeks ago." The remaining 15 patients knew nothing about this near-Eastern place, except for one or two who answered it was a Canal or a geographic name. Two were aware that they had read or heard about it recently, but had forgotten what it was.

When asked whether they had any friends in the hospital, six patients answered negatively, giving some reason why they could not or would not make friends in that place; one said that all the patients there were her friends. The remaining nine could each name at least two fellow-patients whom he or she

considered as a friend, several of them being drawn from the Korsakoff group familiar to the interviewer.

Five patients gave the day's date correctly on one occasion at least, and seven more within two days' margin of error either way. The others were seriously mistaken, even as much as two years behind the time; errors by postdating were rare and much more conservative than those made by patients in the early confusional state of the disease. None of the patients gave an instantaneous correct answer to the question asking his age, but nine replied correctly after a second's delay during which, presumably, they performed some fairly rapid as well as accurate calculation. Their answers, however, were not invariably right on repeated tests, and the typical reply to this question was, like that of Zangwill's (32) two patients, an underestimate ranging from two or three years to over a decade. The magnitude of error fluctuated with some patients on repeated occasions, but tended to vary with the length of hospitalization.

Only a few of the patients knew with even approximate accuracy the duration of their hospitalization, though most of them remembered the year it had begun. Correct or near-correct estimates may have been lucky guesses in some instances, for the same patients were often wide of the mark when answering the same question on another occasion. Four of the patients had kept an exact count of the years or months they had spent in the hospital continuously or before their last discharge and again since their re-admission. The others tended to underestimate the length of time they had been there, the most dramatic example being that of a patient (H.T.) mentioned above who always said she had come in the previous afternoon. On one occasion she was confronted by the experimenter with the truth, *i.e.*, that according to her case notes, which he was perusing, she had been there for four years. Listening to this, she seemed manifestly disturbed for a moment, and then promptly replied, "Well, you are the doctor, you know better," adding after a few seconds "but it feels as if it was only yesterday." In spite of the immediate shock, this incident did not appear to have had any lasting effect on the patient, for on the many occasions she was asked the same question during the following three years, she always answered that she had come in the day before. Yet, if questioned how she spent her days in the hospital, she would describe her work in the sewing room and even on the progress which manifestly spread over several days. If asked to talk about her daily routine, without specific reference to the hospital, however, her answer would be drawn from an earlier setting of her life.

Some suggestions made by Claparède (4), MacCurdy (12), Schilder (18) and Rapaport (15), that the amnesia of Korsakoff patients might be caused by a failure of their emotional involvement in the original experience, is worth considering, even though it could not explain all the memory and learning defects of the syndrome. The literature lists occasional examples of episodes characterized by strong affective involvement being unusually well remembered by Korsakoff patients, though hardly in the manner of deliberate recall. Our observations are not solidly in support of this hypothesis. Of the autobiographical data these patients reported, few were affect-laden or presented with any accompanying sign of emotion. Of course, life in the hospital is not rich in experiences providing for intense personal involvement. Those patients who kept in touch with their families almost invariably knew of any important events which occurred there—the engagement or marriage of a daughter, the drafting of a son, the birth of a grandchild—and a visit home or the call of a visitor at the Hospital on a Sunday were usually well remembered later in the week.

None of the patients could recall the circumstances in which they had first entered

the hospital, but many knew that they were confused and severely ill at the time. Nevertheless, the three women who were readmitted after a short absence, two having been discharged, talked reasonably coherently about the circumstances in which they got back. The third of these, who made repeated attempts to leave without permission, discussed her escapades with malicious glee, and was altogether fond of a little raillery. Yet another woman who often reminisced about her far from respectable past in a tone of mild regret mixed with provocative gaiety, would switch to one of indignation in sounding a complaint about having been deprived of her spectacles, teeth, and money on admission, but more often recited this set piece of grievance rather monotonously; a third who wore the marks of a severe bruise on her calf and shin for several months had only the vaguest recollection of how it happened and could not remember any accident.

The most striking instance of delayed recall of an emotionally-tinged incident occurred when the affect was vicariously experienced. The patients usually rode in pairs from their hospital to the laboratory, and on one occasion M.O.'s partner was a woman who, generally depressed in mood, had at times protested with considerable agitation and anger about her being prevented from rejoining her son. On that occasion she began the experimental session with a fairly vehement complaint, and had evidently spoken about the matter in the car, for as soon as M.O. came to the laboratory she too appealed to the experimenter on behalf of "that unhappy woman who would die of grief or do away with herself unless allowed to leave the hospital." M.O., admittedly, was something of an exception in the Korsakoff group studies, both for her persistence in starting conversations with the experimenter—almost invariably centering on her own, mostly imaginary, physical symptoms—and for providing most of the few instances of fabulation. There was nothing remarkable in her remembering a fellow patient's grievances after the lapse of half an hour, but when two weeks later she came back to the laboratory, that time in the company of another patient, the first thing she did was to ask the experimenter, "Doctor, have you done anything about that poor woman? You know, she will die if you don't let her go!" The incident is of some interest because it was so contrary to expectation; it neither confirms nor does it dispute the argument based on personal emotional involvement.

Perhaps the strongest evidence for the case in our experience was provided by H.B., who tried to relearn a simple nursery rhyme of four lines which she could remember having known as a child. She worked at it for a week, was certain that she had mastered it, but utterly failed in the test. Though she never succeeded in reciting more than the first three words of the verse, she remembered her disappointment for a long time, and would talk about it, perhaps a little shamefacedly but not with any deep emotion. Neither example touches on the question of deliberate recall as distinct from the spontaneous recurrence of memories.

## EXPERIMENTS

Under this heading will be discussed tests of memory and learning which followed a definite instruction to the subject to remember a word, a story, a figure, or to learn some response pattern. Several of the findings listed below will but summarize the results of procedures reported at some length in previous papers of this series.

### RECALL

*Digit and running memory span:* The Korsakoff group's score on Wechsler's *digit retention* test was within the norm of their age group in the general population. If the task was that of reproducing five digits or letters forming the end of a series of indeterminate and varying length, however, these patients performed less efficiently than the controls.

This finding is thought to point to a defect in shifting attention rather than in immediate recall (22).

*Information:* When required to recall isolated units of information, such as a proper name, a date, or an address, the Korsakoff patients varied considerably in efficiency. Some of them could always correctly reproduce a name or address after an hour or a day, others could not even after three minutes. At least one patient who had a fairly good memory for events in his recent as well as his more remote life, could not retain a name, no matter how hard he tried. Immediate verbatim reproduction of single sentences, ranging from three to 12 words in length, was very nearly perfect if these were presented aurally, but visual presentation made for faults in most patients even with a load as light as five or six words.

Few people memorize more extensive verbal material word for word, unless it happens to be poetry, a legal definition, or a magic formula; therefore, the tests of recalling the content rather than the original phrasing of short narrative passages were the more informative about retention and distortion in Korsakoff's psychosis. These processes have been examined in detail (25), and all that can be said about them here is that much of the content is lost in immediate reproduction, and most of that vanishes within the first few hours. It makes little difference to Korsakoff patients whether only the gist of a story is given them, or if the report is elaborated and embellished with unimportant details, for they almost invariably forget the latter as soon as they have read or heard them. Their recall for the last items is no better than for those occurring at the beginning of the text.

*Single words:* The Korsakoff group's recall of lists of isolated words or meaningless syllables is at a significantly lower level than that of the controls on immediate testing, and declines more rapidly over the first few minutes, as shown in Figure 1. Test was by number of items retained by unaided reproduction, since the patients' achievement by learning new associations was even poorer. Allowing more time to memorize the words or offering an opportunity for relearning them (19) did not improve their performance. Errors by calling incorrect words were few on immediate testing, but rose well above that of the alcoholic controls after a delay of three minutes; nevertheless they were almost invariably in accordance with the formal properties of the test words, *i.e.*, nonsense was incorrectly recalled in place of nonsense, meaningful for meaningful material, three letters with a vowel flanked by two consonants for words with the same structure. This much Korsakoff patients seem to have learned incidentally.

*Time span:* Tests of reproducing continua and intervals ranging from two to 30 sec. showed greater inaccuracy in the Korsakoff patients than in either control group (22), but no consistent tendency towards over-or underestimation. Examples of their misjudging longer time spans have been given in the interview material and could be multiplied. In assessing the time spent in an interviewing or experimental session—30 to 90 minutes—their answers were fairly accurate.

*Counting:* In order to test the Korsakoff patients' ability to terminate and resume a continuous task in accordance with a directive, they were instructed to count slowly from one to 22, and this all but one in a sample of 16 could do without error. Then they were told that they would be asked to count on from where they left off up to 37, but would first be given something else to do. When reminded to continue counting, after a task of about three minutes, only four members of the group performed this correctly; two could not remember at all what to do, the others resumed at some point between 18 and 23 and went beyond 40 until stopped by the experimenter, except for one subject who started at one and counted up to 22 again.

*Figures:* The drawings shown in Figure 2 were presented for reproduction to 22 Kor-

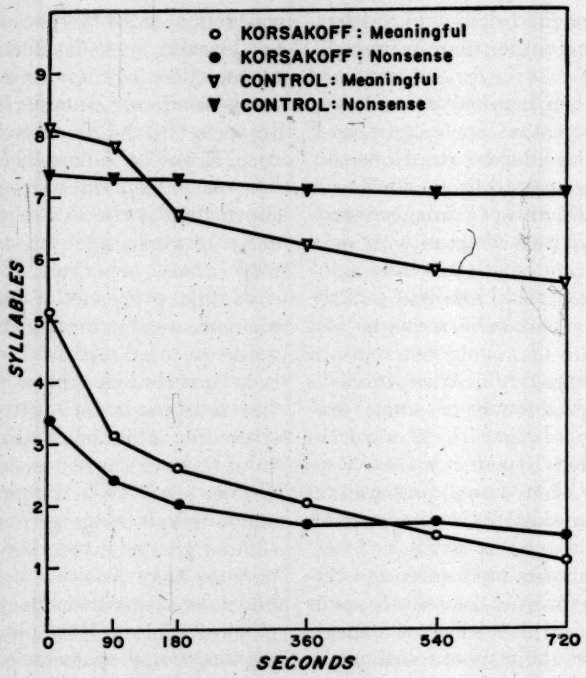


FIG. 1. Recall of meaningful and nonsense material by Korsakoff patients and control subjects.

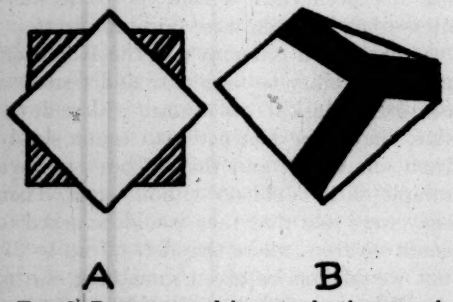


FIG. 2. Patterns used in reproduction experiment (see text).

sakoff patients, 15 alcoholic and 8 neurological controls. Figure A was a red diamond on top of a blue square, Figure B was black, on white ground; both were drawn on cards 3 x 5 in. No limit was placed on inspection time, and subjects were asked to be sure they could well remember the models before testing started. In total achievement no clear differences could be established between groups, since all but one alcoholic control failed to reproduce design B with even approximate accuracy. Distortions of the patterns, however, tended to be grosser, and omission of detail or failure to reproduce anything of a design occurred more frequently in the Korsakoff than in the alcoholic control group. These differences became more pronounced in the subsequent copying test. In this, seven alcoholic controls reproduced both designs correctly, as compared with two neurological controls and two Korsakoff patients.

The most remarkable error of both the latter groups, in reproducing from memory and in copying alike, was an arbitrary use of color. The subjects had four pencils lying before them—black, red, blue, and green—

yet most of them used only one for both designs, most frequently black. Green was used as often as the other colors. Reversal of figure and ground was a common error, and with design B the tendency towards symmetry was very pronounced.

*Experimental tasks recalled:* In one laboratory session which consisted of twelve short procedures, the subjects were asked half way through and again at the end to list as many of the tasks they have been engaged on as they could recall. The means of 16 Korsakoff patients were 2.4 and 2.9 on the two tests, those of 16 controls 4.3 and 6.9, both significantly higher ($t = 4.66$ and Wilcoxon's $T = 29/135$, $p < .01$). The modal response of the Korsakoff patients was three at first and two at the end of the session, and usually—though not invariably—included the last procedure, as well as one or two others of which some visible reminder had remained in sight.

The recognition of test material was not systematically investigated but there occurred at least one remarkable instance of obliviscence, when in an experiment with apparent movement (21), a patient (H.B.) who was shown the picture of a car driving along a road for a fourth time within three min., insisted she had not seen it or its like before; yet the only intervening event was the exposure of some straight lines. Still there were many occasions when patients correctly recognized an instrument and described the procedure it was used for, even after an interval of several weeks.

A controlled study of the Zeigarnik (35) effect, *i.e.* of a preferential tendency to recall uncompleted or unsuccessful performances, showed no consistent trends, largely because Korsakoff patients forget their failures even more rapidly than the tasks themselves. When, following an unsuccessful attempt, they were asked whether they had done well or poorly in the trial, they almost invariably thought they had done pretty well.

RECOGNITION

*Figures:* Several tests of figure recognition have been discussed in detail (22, 23), and here only an elaboration of one will be considered, so designed as to explore any tendency towards normalization (31) in the course of dwindling memory. The 12 figures shown in Figure 3 were presented to 16 Korsakoff patients and 16 alcoholic controls, with the instruction to remember the design marked here (but not in the test) with the letter G. Each design was printed on a card 5 x 3 in., leaving a margin of about 1 in. on either side. The cards were shown in a standard pattern of three rows of four, then removed and displayed for each of the subsequent tests in a different set order of three rows.

Recognition was tested immediately and after intervals of 15, 30, and 60 minutes, during which the subject was kept occupied; on none of the occasions was he informed whether his choice was correct or not. The

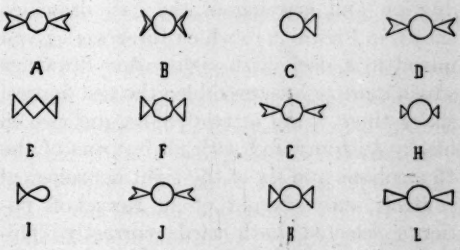


FIG. 3. Figures used for recognition experiment (see text).

TABLE 1
*Progressive Recognition Choices of "Winged" Figure*

| Figure chosen | Korsakoff (N = 16) | | | | Control (N = 16) | | | |
|---|---|---|---|---|---|---|---|---|
| | Immed. | 15 min. | 30 min. | 60 min. | Immed. | 15 min. | 30 min. | 60 min. |
| G | 9 | 5 | 5 | 3 | 15 | 15 | 15 | 15 |
| A | 6 | 8 | 6 | 8 | 1 | 1 | 1 | 1 |
| J | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 |
| F | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| D | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 0 |

selections of the two groups on the four occasions are set out in Table 1, and the only additional information of note is that the errors of the control group were all contributed by one subject who at least chose consistently if incorrectly, while none of the Korsakoff patients made the right choice on all four occasions. Indeed only two chose G a second time, and they subsequently switched to other figures; one persisted with A throughout; all the others shifted at least once or more often in their selection. A tendency towards normalization is certainly consistent with their errors, for A and J are at least one step, F and D two steps in the direction of simpler design. It must, however, be noted that as the experiment had been set up, they could hardly make an error other than by normalizing. No general tendency of a progressive drift towards simpler forms could be detected, though F was selected only in the last two tests following previous choices of G and A.

Another recognition test followed reproduction and copying of the two drawings shown in Figure 2, in which these were given mixed in a deck with eight other drawings which more or less resembled the test figures, six of them being in two colors and two in black. As compared with all but one of the 15 alcoholic and six of the eight neurological controls, only six out of 22 Korsakoff patients selected both cards correctly (chi-square = 14.0, $p < .001$); another six made one correct choice.

*Objects:* On one occasion two objects were shown to the Korsakoff patients, a pencil sharpener and a stapler, with the instruction to name and remember them. All 22 Korsakoff patients correctly named or described the two objects, which were then mixed up with eight other articles made of metal: an ashtray, a pen knife, a counter, a pair of scissors, a screw driver, a compass, a large paper clip, and a punch. After busying themselves with a different task for five minutes, the patients were asked to pick out the two articles earlier shown them, and they all chose both objects correctly.

In a different testing session, 16 Korsakoff patients were shown four objects and asked first to name them, and then to remember them in the same order. The articles were a telephone, a glass of water, a stapler, and a briefcase, placed wide apart in the room. All the subjects correctly named the four objects and recalled them after a minute, but six failed to list them in the original sequence. After an hour's interval, six patients could still list the four items, two in the correct order, one of them having memorized this by means of a formula invented for the purpose.

*Scenes:* The material to be recognized consisted of two fairly complex pictures, the colored covering pages of a magazine, one representing a lady rider as she is being helped off with her boots by a maid in the middle of a heavily period-furnished bedroom, the other the scene of children leaving Sunday school and running up to the cars in which their fathers are waiting. Fifteen Korsakoff patients were shown these pictures at different testing sessions, with the instruction to observe them carefully so that they could remember them. In one instance, alternating both pictures and sequence, they described the scene immediately after inspection, in the other they were prevented from verbalizing their impressions by another task.

The purpose of the experiment was to test, apart from gross recognition and the possible distorting effect of reconstruction, Zangwill's (33) observation about a variety of paramnesia characteristic of alcoholic Korsakoff psychosis. The testing procedure was carefully controlled when the picture was shown a second time after three minutes. First, the experimenter asked the subject if he had seen the picture before; following a positive reply, he then asked, "Is it exactly the same?", and in case of further confirmation, "Are you quite sure it is the

same?" In spite of this considerable counter-suggestion, there were only six instances out of a total of 30 tests in which a subject wavered from absolute certainty, none of them on both occasions. The wording typical of the 24 standard responses was, "yes . . . the same . . . quite sure, "while the exceptions were: "Little different," "color lighter," "mostly same," "was it more finished?," "not so many children," and a single "No." These answers were equally split between the two pictures, first and second test, recall with and without description, and all but the last were given in response to the second question, "Is it exactly the same?" Although asked in what way the picture was different, if thought to be so, the six subjects gave no details beyond the brief remarks quoted above.

LEARNING

*Pegboards:* The procedure was based on the Rey-Davis performance test (16, 34), and used two sets of four boards 6 x 6 in. On each board there were three rows of three cylindrical pegs, ¾ x ¾ in. spaced 1 in. apart. Eight pegs were glued to the base, one could be lifted out of its socket and the position of this varied from board to board, being at top left, center of middle row, top right, and center of bottom row, from left to right facing the subject. One set of boards and pegs was plain wood, the other was painted; the base white, the pegs three in one color, two pairs in two different colors varying from board to board, and one each black and in the fourth color. The last was the loose peg, red, yellow, green, and blue in order from left to right. The subject was presented with the colored boards first, and told that one of the nine pegs could be lifted up, the others were firm. His task was first to discover the loose pegs by trial and error, and then to remember which one it was on each board.

Up to ten trials were allowed to test his success in learning, which was achieved when he performed the task faultlessly twice in succession. After completion of this test, the four boards were each turned to different angles, 270°, 360°, 180°, and 90°. The experimenter explained what he was doing, and the subject was allowed to watch while he rotated the boards. Although at this stage only faultless performance on first trial was recorded as success, the subjects were nevertheless allowed to experiment up to ten trials if they failed on earlier ones. Following this, the boards were turned back to the original position, and the same procedure followed as before. Next came the test with the unpainted boards which, at first, were laid out in the basic position, and the subject was informed that each of these was identical with the colored board it replaced, and that the loose pegs were in the same position as in the last test. The procedure was the same as the first with the colored boards, but after this the boards were rotated uniformly, first by 90°, then by 180°, and finally back to the basic position. In each position the test terminated with successful learning or the tenth trial.

The criterion of learning in each test was correct first choice on all four boards in succession from left to right, twice running; the criterion of successful transposition of learning was the same on first and second trial. The results and probability levels of differences between the two groups, as given by Fisher's Exact Test, are presented in Table 2. One half of the Korsakoff group was able to learn the color sequence, and several of these patients retained this after rotation, but only one remembered the position sequence, and of the three more who could learn the latter none was able to transpose the pattern. The difference in difficulty between the two parts of the experiment proved narrower for the controls, several of whom transposed successfully after rotation, though only a few learned the position sequence while the apparently easier color sequence provided sufficient information.

TABLE 2

*Successful Learning (L) and Transposition (T) with Pegboards*

| Position | Colored | | | Plain | | | |
|---|---|---|---|---|---|---|---|
| | Basic (L) | Rotated (T) | Basic (T) | Basic (T + L) | 90° (T) | 180° (T) | Basic (T) |
| Korsakoff ($N$ = 16) | 8 | 5 | 5 | 1 + 3 | 0 | 0 | 0 |
| Control ($N$ = 16) | 15 | 10 | 11 | 5 + 11 | 9 | 8 | 5 |
| $p$ | 0.01 | 0.08 | 0.02 | 0.09–0.01 | 0.0004 | 0.001 | 0.02 |

While most of the Korsakoff patients could learn the position of the first two loose pegs, they often confused the third and fourth, or chose randomly on the last two boards. The controls, when unsuccessful, tended to pick three of the loose pegs on first choice and the fourth on second, the latter occurring most frequently on the second or third board.

*Incidental learning:* The shift from colored to plain pegboards tested incidental learning if a subject solved his problem by learning the sequence of colors, but incidentally also paid attention to their position. A more direct test of incidental learning proceeded by means of a special jig saw puzzle. The pattern to be assembled was a 66 words long newspaper report rich in small items of content. It was printed on cardboard in ⅜ in. letters spreading over six and one-half lines. At various points six identical windows were cut into the print, so that each cut across two adjacent words in two or three lines. The cards thus obtained were handed to the subject with the board, and he was instructed to fit each into its proper window. It was also explained to him that he could easily find the proper fit by checking that words reassembled made sense, but no further instruction was given. When he had fitted all six windows, he was asked whether he had finished with the material, and it was removed from his view if the answer was in the affirmative. He was then asked to repeat all that he remembered about the story printed on the cardboard. Every one of the 16 Korsakoff patients and the 16 alcoholic controls solved the puzzle without error, the former taking somewhat longer over it but none more than 150 sec. The means of the items reported were .75 in the Korsakoff and 3.69 in the control group; the difference is significant with $t = 2.77$ ($p < .01$). Of additional interest were the reports of the subjects on questioning, according to which all but four subjects, three controls and one Korsakoff patient, read only the words which gave him clues, not the content. The highest score of the control group, 11, was achieved by a subject who read for content, but the best record in the Korsakoff group, 6, belonged to a patient who said he had not.

*Choice reaction:* Subjects were seated in front of a Gerbrands tachistoscope with a telegraph key in comfortable reach of their right hand and a pedal at their right foot. Pressure on one lit up a green, on the other a red light facing the experimenter. The task consisted of five series, each involving a different level of difficulty in discrimination; the load, however, was varied only on the input side in series I to IV. Simple geometrical figures were used for signals, which were shown on cards to the subject before each series so that he could become familiar with them. They were presented through the tachistoscope, with an exposure of .6 sec. which was well above the subject's threshold of recognition, and if asked to the experimenter displayed a figure a second time. Each series followed a standard schedule within which the presentation of the figures was randomized, each occurring the same number of times as the others, both in the

first and the second half of the schedule. Throughout the first half the subjects were told after each response whether it was right or wrong, in the second half no information was given.

Series I involved only two figures, a triangle and a cross, each shown ten times, and calling for a response with the key to the one, with the pedal to the other. Series II added a circle to the first two figures, and to this the right response was with the key; each of the three figures was shown eight times. In Series III, triangle and circle continued to be signals for finger response, while two new symbols, star and square, became the signals for foot reaction. Each figure was shown seven times. Series IV consisted of 36 presentations equally divided among six figures, a diamond being added to those previously shown and bringing up the number of symbols for finger response to three. Series V presented triangle, square, and shield, each eight times, the responses to the first two being the same as before, and the instruction for the shield was to make no response at all. Response latency was not timed, and only unusually long delays were recorded; errors spontaneously corrected by the subject were entered as correct response, changes in the reverse direction as errors. Error scores are given in Table 3 for 18 Korsakoff patients and an alcoholic control group of 18. Since instances of delayed reaction were too few in either group to warrant analysis, the error scores indicate the significant differences between their levels of achievement; the leap from series II to III marks the limit beyond which Korsakoff patients cannot carry instructions efficiently. In the simplest tasks, *information transmitted* was equal in both groups with a mean $T$ of .81. As the number of symbols to be discriminated increased to three and then to four, *information transmitted* also increased in the control group, reaching its peak in series III; in the Korsakoff group, however, *information transmitted* steadily decreased, hitting its lowest in series III. The confusion that set in beyond that in most Korsakoff patients was quite apparent simply from watching their performance.

TABLE 3

*Mean Errors in Choice Reaction*

| Series | I | II | III | IV | V |
|---|---|---|---|---|---|
| Korsakoff ($N$ = 18) | 1.7 | 1.5 | 7.2 | 11.0 | 4.0 |
| Control ($N$ = 18) | 0.3 | 0.2 | 0.6 | 1.6 | 0 |
| Wilcoxon's $T$ | 274 | 325 | 212* | 199½* | 180* |

* $p < 0.01$.

The results were also examined with a view to determining any learning effects. Since the cross and the triangle were shown in every one of the first four series, and each was constantly associated with the same response, practice with these might have shown effects in the later series, as compared with the newly introduced symbols. In series II and III, the Korsakoff patients showed a slight learning effect, but in series IV they made errors in response to the relatively unfamiliar circle only half as frequently as either to the much practiced triangle or to the entirely novel diamond. In series V, out of their total errors of 56, 25 occurred with the triangle, and only 18 with the shield, which was both a new figure and called for a new type of response. Neither were the control group's errors any more consistent with a learning effect. None of the subjects in either group showed a marked preference for responding with foot or finger.

*Conditioning:* The experiment was attempted with 16 Korsakoff patients, using eyelid closure as a response, an air puff as the unconditioned (US), a buzzer as the conditioned (CS) stimulus. A modified version of the apparatus described by Franks and Withers (5) was used, in which the buzzer started an electric clock, and lowering of the eyelid stopped it by activating a photoelectric cell. US and CS each lasted

about .5 sec. and were divided by an interval of .3 sec. A pre-test of five consecutive presentations of the buzzer was given each subject so as to determine that he would not lower his eyelid in response to the sound alone. If he did, the procedure continued until this effect ceased, the criterion of its elimination being five consecutive buzzer signals without subsequent eyelid response. The conditioning schedule followed a standard randomized design of 30 reinforced and 30 unreinforced buzzer signals, the former being more closely spaced in the first half and neither running in series longer than three. Two criteria of conditioning were considered: 1) eyelid response within .3 sec. to five of the first six unreinforced buzzer signals following the schedule; and 2) response within .2 sec. to more than 50 per cent of the unreinforced signals forming part of the schedule. The criterion of extinction was the absence of eyelid response to nine out of ten consecutive unreinforced buzzer signals following the schedule.

Eleven patients satisfied the first and all the remaining five the second criterion, but only four members of the group satisfied both. This suggests that those who conditioned more slowly retained the effects somewhat longer but not for very long. Like Gantt's (7) subjects in a similar test, all the 11 patients extinguished very quickly with a mean of 7.8 unreinforced buzzer signals. Only four control subjects were tested for conditioning; all satisfied the first criterion, three met the second criterion and all took longer to extinguish.

## DISCUSSION

In the literature of Korsakoff's psychosis there has been considerable controversy about the nature of the amnesic symptoms, debating whether they should be attributed to a defect of memory or of registration, to faulty retention or to inefficient recall. These differences reflect a literal interpretation of the trace theory of memory, according to which intact remembering involves three more or less distinct processes, registration, retention, and recall, and malfunctioning of any one would result in forgetting. Of course, the sequentially later processes can hardly function well if the earlier ones do not.

Observations made on Korsakoff patients rarely fit any one of the positions based on this theory, since none of these hypothetical functions is always and consistently disturbed, though on the average they all show some damage. Names or other data do not register or, if they do, they cannot be relied on to be retained, and may be inaccessible on one occasion and nevertheless available at a later time, thus suggesting a failure of recall. In cases of retroactive amnesia, impressions which had been registered before the onset of the disease cannot be recalled, and the verdict seems to favor the argument for a disturbance in recall, but other events can be recalled at will quite efficiently, and the explanation must resort to some selective retention disorder. Unfortunately, the rules by which the selection proceeds have not been discovered, except that events following the onset of the disease are unlikely to be recalled on purpose, while those dating back to childhood are the most likely. This is a rule common to most amnesic conditions. Affect, personal involvement, or interest are not very helpful concepts for predicting the probability of recall.

The inability of Korsakoff patients to keep a correct count of time or of the passage of events is beyond doubt. Repeatedly encountered and closely similar experiences tend to telescope into a single event, and with them the scale along which they would be spaced also collapses; time loses depth. But there are more ways than one to account for this phenomenon. First, while its significance in the mental disorder characteristic of the Korsakoff syndrome is acknowledged, it should also be remarked that the defect is neither absolute, nor always equally apparent even in the same patient; it varies in severity from one occasion to the next, from one context of the

discourse to another, it is slight and often barely noticeable in the judgment of shorter spans but marked for longer periods. Our observations are more in line with Bernard's (2) view that Korsakoff patients have not lost their 'intuition' for the flow of time than with van der Horst's (10) opposite argument postulating a special sense which registers the flow of time directly, *i.e.* apart from events, and which marks the latter with temporal signs. Horst and some other students of the amnesic syndrome would account for all its mental symptoms by a breakdown of the process which impresses experiences with temporal signs.

True enough, Korsakoff patients are notorious for frequently registering events without accurate chronological placement or correct sequential ordering, but this could happen because they are perceived apart from a context. A healthy subject is more exact in, *e.g.*, recalling the number of times he has seen the experimenter, not because the latter appeared to him so very different a person on each occasion, marked with different "temporal signs," but probably because every visit to the laboratory occurred within a different sequence of events framing it, and was distinguished by a different set of experimental tasks. The organism undoubtedly is equipped to scan memories of these events very rapidly, and can thus provide the information necessary for a correct reply to the question, "How many times have you . . . "; it is unlikely to keep special ledger entries for the emergence of any possible question of this type, and to bring its records up to date continuously in the form of so many discrete traces.

The scanning mechanism hypothesized need not be conceived as corresponding to any familiar electronic model, or to any known neural process. It implies that the organism is normally in a state of activity which is not random, which indeed follows programs, conditional and unconditional, and which every so often reaches a momentary pause with an event of matching, recognition, completion, or some other form of closure. Defects in such a complicated mechanism could occur at several phases. The dysfunction characteristic of the Korsakoff syndrome is attributed to the most general activating operation determining the rate, range, or persistence of scanning. This formulation seems to be most consistent with the observations that Korsakoff patients, though they may respond efficiently enough, hardly initiate action, and are exceptionally ready to settle down with unsolved or incorrectly answered problems (24), that—in formal terms—their cognitive functions are maintained at looser levels of tension than in the normal organism.

Direct evidence of inefficient scanning can be discovered in the Korsakoff patients' performance in certain tasks of perception, problem solving and recognition. By hypothesizing its involvement in all cognitive processes, several other observations made on these patients fall into place. This would explain how it happened that our patient H.T., whose conversation was usually sensible even though disoriented for time, nevertheless placed the day of the interview in May, while in her view through the window the ground was deeply covered with snow. The model of defective scanning mechanism fits several theoretical formulations of the amnesic syndrome, *e.g.*, Pick's (14) remark about the patients' failure to check their thoughts, Lidz's (11) suggestion that their trouble is an inability to select the proper recollection from a 'number of alternatives,' and our various experimental findings (22, 23, 26) concerning their rigid sets, their difficulty in changing an orientation first adopted toward an object or situation to be perceived, or toward a problem to be solved.

The hypothetical scanning process is also closely related to the traditional psychological construct of recognition. Scanning stops momentarily, prior to turning toward a new target, when recall is achieved. Its activity depends not only on the mechanism which

keeps it going, but also on some such process as recognition for direction and for the termination of its phases. If the activity were insufficiently sustained it would be prone to close prematurely, with incorrect recognition. Many examples of the Korsakoff patients' defective behavior seem to accord with this formulation.

Anomalies of recognition in these patients, however, may also arise from a failure in relating some information to the experiential self. Claparède's (4) case is the classic example, that of a woman who refused to shake hands with him for fear that she might be pricked with a needle. In fact precisely that had happened to her when shaking hands with him earlier, but this experience she had completely forgotten. All she could say in justifying her suspicion was that the thought this might happen had crossed her mind, for people sometimes do conceal pins in their hands. Claparède's explanation of this incident, in terms of the patient's failure to relate events personally experienced to the self, does not appear very helpful, for it inevitably enmeshes the construct of recognition in a theoretical model which raises more questions than it answers.

Still, it is not without some significance that the study of the amnesic syndrome should repeatedly have led various observers to a theoretical formulation of this type. Of the several theories suggesting a divorce between experience and consciousness as a characteristic of the amnesic syndrome, perhaps the most instructive are those (2, 6, 17, 28) which liken perception as well as memory in Korsakoff's psychosis to dream states. Recognition in Korsakoff patients is undoubtedly often, if not always, characterized by a weaker sense of reality and certainty than in normal persons, as is normal dream information. Since dreams are virtually outside the structure of ordered experiences, the analogy also agrees with our hypothesis of contextual isolation, but an examination of the balance between centrally and externally initiated neuropsychological processes furnishes adverse evidence. In dreams the scanning operations are extremely rapid and control by sensory input is relatively low; in the Korsakoff syndrome the balance appears to be tilted in the opposite direction.

A special construction could reconcile this difference between cognitive functions in dream and in amnesic states. If certainty of recognition and the, by hypothesis at any rate, concomitant sense of reality is that attribute of experience which establishes it within the context of other experiences, this attribute may be reduced alike by a deviation from the normal balance between central and external control in either direction. The same reasoning could be extended to information which is not consciously experienced, and the term recognition too would include various implicit processes of matching and task completion.

In the wider sense, recognition closes each phase of behavior at all levels of functioning, from motor to problem solving. Recognition, even in the narrower and customary sense of the word, forms the final phase of recall and of reproduction. Consequently, though instances of paramnesia in recognition did occur in interviews with our Korsakoff patients, neither they nor the experimental results presented above would justify a distinction between the functions of recognition and of recall in the analysis of the amnesic syndrome. An operational distinction of the two performances, however, can be made. In our study, as in Nyssen's (13), it was apparent that the impairment shown by Korsakoff patients was consistently milder in tests of recognition than in situations requiring voluntary recall, and in the former at times it was not noticeable at all. This difference in performance also points to a defect in a general mechanism of activation as a likely common source of the psychopathological symptoms in Korsakoff's disease.

Indeed, it is questionable whether the

memory and learning disorder in all its various manifestations ought to be considered in isolation, even though this is the distinctive attribute of Korsakoff's psychosis. Previous reports have demonstrated anomalies characteristic of the amnesic syndrome in perception, concept formation, spontaneity and activity rate, on tasks which did not involve memory functions. These defects, of course, are not specific to the Korsakoff syndrome in the manner that the amnesic symptoms, or at any rate their relative severity, are. Still, they form part of the syndrome, and tend to vary in gravity with the latter; the psychological damage affects all cognitive functions in this disease, not memory exclusively.

It should be remembered that while the general trend showed some of our Korsakoff patients to be more efficient or successful than others in most tests—in manual skill, speed, perception, concept formation, problem solving, and persistence alike—the correlations between scores on any two tests were not high in most instances; the bulk fell in the low positive or moderate range, many came close to zero, and quite a few were negative. The same observation applies even if the universe of tests is restricted to those probing primarily or exclusively various aspects of memory or learning. The comparison of one patient with another, or one set of patients with another, would therefore be no more instructive about their amnesic disorder than about their more extensive cognitive impairment. Both are best studied by contrasting the entire sample of Korsakoff patients either with the normal population, as will be done in the examination of the interview material, or with a control group which, in one respect or another, differs from the general population in the same way as the Korsakoff patients do. This has been our rule for most experimental procedures.

The conclusions that can be drawn from the various findings discussed in some detail or more summarily in the earlier sections of this paper are as follows.

The Korsakoff patients studied all knew their own names and had some memories of their pre-morbid life, but these were poorer in quantity and content than would be found in healthy men and women of the same age, and tended to be reported in stereotyped phrases. Their memories of more recent and current events were scantier yet, more restricted than could be accounted for by their impoverished social setting alone. They were reasonably well oriented in space, knew where they were, and could find their way about; on occasions they were fairly well oriented in time, but had usually lost count of the years and condensed long spans of time. They showed a strong tendency to telescope repeated occurrences of similar events into one or two occasions.

Immediate testing of memory span, if it allowed for an echoic automatic reproduction, did not show a deficit. If the material consisted of novel combinations or was itself unfamiliar, however, particularly if it was meaningless, or if the test entailed a transposition from one sense modality to another, the Korsakoff patients' immediate recall proved to be abnormally low. Their rate of forgetting was much steeper than the normal for all types of material, and rapidly reached the zero level. The same observations also apply to conditioning; most of the patients showed some effects of conditioning, and all extinguished very rapidly. They could follow instructions for a considerable length of time, as long as their load of information was below a certain critical limit and the task was continuous.

The Korsakoff patients' learning capacity was very slight, and their ability to transfer learned associations to similar tasks was negligible. Incidental learning did occur with them but was less reliable than with the controls. They were capable of establishing new associations as long as these were simple and were presented in very small

doses. Their rate of forgetting does not seem to be related to the interference of other learning or of irrelevant information. There is no strong evidence that emotional involvement counteracted or reduced the amnesic disturbance, and none that absence of affect caused it or that some motivated forgetting such as repression could account for it.

Some of the Korsakoff patients at times showed genuine concern about their poor memory; others, when asked how it happened that they had forgotten simple things one would expect them to remember, pleaded lack of interest or too deep involvement in other concerns. While there is no reason to believe that they were really deep in thought about other matters while reading, observing, or being told something, their want of interest seems true enough. It could be observed in a lack of spontaneity, and in that any interest aroused in them reactively seemed to flag as soon as the information to be absorbed or communicated had passed a critical and relatively low level. On the other hand, they often showed considerable interest in their achievement on an experimental task, though this frequently happened when they believed that successful performance might shorten their hospitalization. As mentioned earlier, they were not sufficiently involved in their tasks to remember even for a short while whether they had performed it well or had completed it, neither did they resume unfinished problems (24).

Attention is, perhaps, even more ambiguous a term than interest. In the sense of sticking to a task, Korsakoff patients could attend to repetitive jobs as well as anybody, but when their attention had to be constantly shifted, as in listening to a story, they soon lost its thread and manifested no attempt to pick it up again. In the sense of observing cues which were not explicitly pointed out to them, *e.g.*, the colored pencils in the figure drawing task, they showed very poor attention. They could listen to and follow instructions, and were exceptionally impervious to any distraction by noise or incidents occurring in their surrounding. In tasks demanding a divided attention they performed poorly.

The present research on the memory functions in Korsakoff's psychosis, like that of so many previous investigations, has produced more paradoxes than resolutions—has raised rather than answered questions. We have thus an added reason for reconsidering the cognitive anomalies of the Korsakoff syndrome reviewed in previous reports. The salient findings have concerned the patients' inefficient selective operations in perception and concept formation, their relative incapacity to change sets they had initially adopted, and their failure to integrate sequential impressions into unitary structures. The first of these undoubtedly hampers learning or memorizing at the perceptual level, for it is difficult and often impossible to remember something indistinct or loosely defined. The significance of rigid sets for the processes involved in remembering has been touched on above; this defect clearly impairs the efficiency of acquisition as well as recall. A failure in sequential integration may, however, be the defect most directly concerned with the amnesic condition.

The external environment impinges on the organism in discrete stimuli or spatial patterns, and these are integrated into structures of various lengths and complexity. The slow unfolding of a Japanese paper flower in a dish of water is no less a unitary experience than the sudden course of a shooting star. There must be a central process within the brain which imposes structures on collections of impressions, and if this were completely absent the organism would fully conform to Bürger-Prinz and Kaila's (3) description of the Korsakoff patient as consisting of cross sections without a longitudinal dimension. Many patients in the early phase of Wernicke's disease correspond closely enough to this model. The typical Korsakoff patient is at some point

between this extreme and the normal, yet in him too the central process fails to reinforce those lower order neural systems of perception and immediate recall which, if reinforced, would be structured into the higher order systems of lasting memory. In Hebb's (9) terms, the Korsakoff patient's brain can form cell assemblies but not phase sequences.

As far as psychological theory is concerned, this model has the advantage of admitting the several paradoxical occurrences in the amnesic syndrome. The cell assembly is a structural change in the brain; it is not lost but is not easily accessible. The model accounts for the occasional examples of accurate recall or learning, often following previous failures; it is but a reinterpretation of the argument that the amnesic syndrome represents a defect in recall rather than in retention. It explains why registration, tested by immediate recall, is undamaged, and that memories out of reach for voluntary recall can emerge spontaneously, and those that had been well established earlier are no longer reliably available. For the memory systems are not so many self-contained structures, each separately connected with a central point, but a complex network of facilitatory and inhibitory patterns, any one of which can be reached along several courses but only by crossing some intervening regions.

In a vastly simplified diagram, translating dynamic systems into plane geometry and taking an ideal rather than an actual example of the amnesic syndrome, the latter can be likened to a torn spider web at one end of which the insect hangs on a single thread. It can get back to the remnants of the web along that single path and travel across the tattered remains of the web, but it can spin no new threads either to repair the damage or to expand its original orbit. If the patient can get a foothold in the memory system of his past, and he usually can do that, other memories which are collateral also become available. But the thread, which may be regarded as representing consciousness or the self, has no collaterals. The patient's impressions registered in the recent past lacked that reinforcement which would have structured them into stable systems (20), they have remained isolated, though possibly some strong affect accompanying their registration may have structured them into its own preexisting system.

The foregoing metaphor should not be followed too closely, for it is certainly not meant to explain the amnesic syndrome in terms of a special self system or of an insufficiently defined construct of consciousness. The model proposed consists of a plurality of interacting systems in which the organism classifies information; their subordination to a central system, *i.e.*, one corresponding to the self, is not a necessary postulate. Each system is thought of as integrating sequentially the items of information belonging within its frame of reference, and these items, whether consciously experienced or otherwise registered by the organism, are simultaneously embedded in several systems. Last Sunday's cocktail party at Bill's house will be filed under *Bill*, under *Sundays*, under *going out*, and subheading *afternoon parties*, and also under *physics*, *Siam*, and *Jury system*, if one happened to have discussed the latter topic, or have had an unusual encounter with a physicist or met a visitor from Siam on that occasion.

The model proposed thus dispenses with the postulate of special temporal signs, for the sequential position of any constituent item within a system is determined, and since the various systems intersect it is sufficient that a reference in time be given in one or another. It is reasonable to hypothesize that all these reference points form a system of their own, but that need not entail a special sense for the immediate apprehension of the flow of time, as van der Horst suggested (10). In its properties here outlined, the model advanced clearly differs from Bartlett's theory (1), as it does in

various other aspects, but similarities between the two will also be apparent. Both Bartlett's and the present attempt to construct a paradigm of remembering draw their evidence from the analysis of other cognitive processes as well as of the more specifically mnemonic operations; both develop Head's construct of schemata, which implies that "every recognizable change enters into consciousness already charged with its relation to something that has gone before . . . " (8, p. 605). Both theoretical models also extend this principle, originally applied only to the body schema, to every type of information the organism carries, not only the postural or that which refers to the self.

Our model building must therefore be pursued a step further, so as to pull together the major cognitive defects found in Korsakoff's psychosis under one theoretical construct. All sensory information is organized in accordance with the momentary expectancy; incoming stimuli are monitored by but also modify ongoing neural processes. The balance between the two effects is primarily a function of the situation, but may also be determined by such stable factors as a brain lesion or a personality disorder. A loud bang has greater information value in a reading room than in a forge; it—or at any rate an unexpected message of a somewhat less penetrating intensity—also exerts a smaller impact on Korsakoff and other brain damaged patients than on healthy persons. These patients, as has been observed, are less able than normal men and women to perceive in a manner inconsistent with their expectancy or to change their set. This may indeed also be the reason for their tendency to perceive fewer aspects or distinctive attributes of an object or a situation, and for their duller selective processes. Moreover, expectancies are confirmed or negated by the sensory input, and are accordingly sustained, modified, or replaced by other expectancies. Quite conceivably, the sequential structuring of discrete impressions into unitary experiences proceeds by means of these concatenations.

An impairment of that central neural process which corresponds to the arousal, maintenance, and modification of expectancies could thus be at the root of the Korsakoff patient's mental disorder. The scanning mechanism considered earlier is so conceived as being involved in this process. Furthermore, it is also plausible that the centrifugal impulses and the "non-specific, activating" system of the brain are concerned with this process.

Recent extensions of our knowledge of brain physiology have offered to the student of behavior an unprecedented freedom for speculation. Like all true liberty, this also carries with it an obligation, and the psychologist should not be blamed for venturing far in building his models. Still, he must observe certain boundaries, those set by the established facts of anatomy and physiology. The neuropathology of Korsakoff's psychosis is fairly well documented; most reports associate the amnesic syndrome with damage in the mammillary bodies, and records of very similar mental symptoms have been observed with bilateral lesions of the hippocampal gyrus or the fornix. Whether the neuropsychological systems hypothesized in our analysis of the Korsakoff syndrome are compatible with its neuropathology is yet to be determined. This is the point at which the psychological study reaches its limit.

## SUMMARY

Various memory functions and learning capacities of a group of chronic Korsakoff patients were investigated by means of structured interviews and experimental procedures. The findings are presented and discussed in relation to certain theoretical formulations of the mental deficit in the amnesic syndrome. A theoretical model is proposed which accounts for other cognitive defects as well as the amnesic symptoms of the Korsakoff syndrome.

## REFERENCES


1. BARTLETT, F. C. *Remembering*. Cambridge Univ. Press, Cambridge, 1932.
2. BERNARD, P. Essai psycho-pathologique sur le comportement dans le syndrôme de Korsakoff. La Raison, **2**: 93–101, 1951.
3. BÜRGER-PRINZ, H AND KAILA, M. Über die Struktur des amnestischen Symptomenkomplexes. Ztschr. f. d. ges. Neurol. u. Psychiat., **124**: 553–595, 1930.
4. CLAPARÈDE, E. Recognition et moiïte. Arch. de psychol., **11**: 79–90, 1911.
5. FRANKS, C. M. AND WITHERS, W. C. R. Photoelectric recording of eyelid movements. Am. J. Psychol., **68**: 467–471, 1955.
6. GAMPER, E. Schlaf-Delirium tremens-Korsakowsches Syndrom. Ztschr.f. d. ges. Neurol. u. Psychiat., **51**: 236–239, 1929.
7. GANTT, W. H. AND MUNCIE, W. Analysis of mental defect in chronic Korsakov's psychosis by means of conditioned reflex method. Bull. Johns Hopkins Hosp. **70**: 467–487, 1942.
8. HEAD, H. *Studies in Neurology*. Frowde and Hodder & Stoughton, London, 1920.
9. HEBB, D. O. *The Organization of Behavior*. Wiley, New York, 1949.
10. HORST, L. VAN DER. Über die Psychologie des Korsakowsyndroms. Monatschr. f. Psychiat. u. Neurol., **83**: 65–83, 1932.
11. LIDZ, T. The amnestic syndrome. Arch. Neurol. & Psychiat., **47**: 588–605, 1942.
12. MACCURDY, J. T. *Common Principles in Psychology and Physiology*. Cambridge Univ. Press, 1928.
13. NYSSEN, R. Contribution expérimentale à l'étude de l'amnésie de fixation dans la maladie de Korsakow d'origine alcoolique. Acta neurol. et psychiat. belg., **57**: 639–666, 1957.
14. PICK, A. Beiträge zur Pathologie des Denkverlaufes beim Korsakoff. Ztschr. f. d. ges. Neurol. u. Psychiat., **28**: 344–383, 1915.
15. RAPAPORT, D. *Organization and Pathology of Thought*. Columbia Univ. Press. New York, 1951.
16. REY, A. D'un procédé pour évaluer l'éducabilité. Quelques applications en psychopathologie. Arch. de psychol., **24**: 297–337, 1934.
17. SCHEID, W. Zur Pathopsychologie des Korsakow-Syndroms. Ztschr. f. d. ges. Neurol. u. Psychiat., **151**: 346–369, 1934.
18. SCHILDER, P. *Mind: Perception and Thought in Their Constructive Aspects*. Columbia Univ. Press, New York, 1942.
19. TALLAND, G. A. The interference theory of forgetting and the amnesic syndrome. J. Abnorm. & Social Psychol., **59**: 10–16, 1959.
20. TALLAND, G. A. A microgenetic approach to the amnesic syndrome. J. Abnorm. & Social Psychol. In press.
21. TALLAND, G. A. Perception of apparent movement in Korsakoff's psychosis. J. Personality, **26**: 337–348, 1958.
22. TALLAND, G. A. Psychological studies of Korsakoff's psychosis: II. Perceptual functions. J. Nerv. & Ment. Dis., **127**: 197–219, 1958.
23. TALLAND, G. A. Psychological studies of Korsakoff's psychosis: III. Concept formation. J. Nerv. & Ment. Dis., **128**: 214–226, 1959.
24. TALLAND, G. A. Psychological studies of Korsakoff's psychosis: V. Spontaneity and work rate. J. Nerv. & Ment. Dis., **130**: 16–25, 1960.
25. TALLAND, G. A., AND EKDAHL, M. Psychological studies of Korsakoff's psychosis: IV. The rate and mode of forgetting narrative material. J. Nerv. & Ment. Dis., **129**: 391–404, 1959.
26. TALLAND, G. A. AND MILLER, A. Perceptual sets in Korsakoff's psychosis. J. Abnorm. & Social Psychol., **58**: 234–240, 1959.
27. VICTOR, M., TALLAND, G. A., AND ADAMS, R. D. Psychological studies of Korsakoff's psychosis: I. General intellectual functions. J. Nerv. & Ment. Dis., **128**: 528–537, 1959.
28. WIECK, H. H. *Zur Psychologie und Psychopathologie der Erinnerungen*. Thieme, Stuttgart, 1955.
29. WILCOXON, F. *Some Rapid Approximate Statistical Procedures*. Am. Cyanamid Co., New York, 1949.
30. WILLIAMS, M. AND ZANGWILL, O. L. Disorders of temporal judgment associated with amnesic states. J. Ment. Sci., **96**: 484–493, 1950.
31. WULF, F. Über die Veränderung von Vorställungen. Psychol. Forsch., **1**: 333–389, 1922.
32. ZANGWILL, O. L. Disorientation for age. J. Ment. Sci., **99**: 698–701, 1953.
33. ZANGWILL, O. L. On a peculiarity of recognition in three cases of Korsakow's psychosis. Brit. J. Psychol., **31**: 230–248, 1941.
34. ZANGWILL, O. L. Some clinical applications of the Rey-Davis performance test. J. Ment. Sci., **92**: 19–34, 1946.
35. ZEIGARNIK, B. Über das Behalten von erledigten und underledigten Handlugen. Psychol. Forsch., **9**: 1–85, 1927.

# PUPILLARY REACTIVITY AS A MEASURE OF ADRENERGIC-CHOLINERGIC MECHANISMS IN THE STUDY OF PSYCHOTIC BEHAVIOR

LEONARD S. RUBIN, PH.D.[1]

Various measurements made of the response to stress have employed the following variables which reflect autonomic activity: pulse rate, blood-pressure, skin circulation and response to adrenalin (4, 13). The results of these studies indicate that chronic schizophrenic patients are less reactive than healthy people. When a large series of measurements is made of basal metabolic rate, circulation rate, body temperature, excretion of 17-ketosteroids, thyroid activity and water metabolism in schizophrenics and in healthy subjects, it is found that the variance of the measurements is significantly greater for the schizophrenics (16). These studies suggest that a concomitant of schizophrenia is some disorder of homeostasis; a disordered response to stress. Symthies (20) recognizes that the onset of schizophrenia is commonly linked to some specific stress, "perhaps a battle stress, or emotional, interpersonal, or biological stress." At this point the present writer would introduce his theory by restating the above quotation. The onset of a functional psychosis, it is claimed, may be commonly linked to a *disordered response* to stress; *i.e.* a sudden emergency which is experienced as a threat to the physical or psychological well-being of the organism. Since Cannon's formulation of his Emergency Theory of Emotion, it has been generally accepted that when an organism is confronted with a sudden emergency the resulting massive autonomic response is functionally adaptive. Specifically, a massive and complete mobilization is achieved by the sympathetic division of the autonomic nervous system with the resultant secretion of great quantities of epinephrine and norepinephrine. Or, as Grenell states in Fulton (7) "The so-called 'fight, flight, or fright reaction' is a product of *maximal* generalized sympathetic activity." The role of the para-sympathetic autonomic during the emergency reaction has been conspicuously neglected and relegated to the protection, conservation and restoration of bodily resources. The hypothesis here offered is that the requisite *maximal* generalized sympathetic activity following the perception of threat is facilitated by a *decrease* in para-sympathetic outflow in normal, healthy people. It is conjectured that were para-sympathetic outflow to increase or to remain at the level of non-stressful states during the time the organism is mobilizing for an emergency that the net sympathetic response would be less than maximal. As a corollary, it is inferred that the "disordered responses to stress" which characterize the functional psychoses consist of significant departures from this characteristic interaction of the adrenergic and cholinergic components of the autonomic nervous system during stress.

It is further hypothesized that the disordered response to stress in the functional psychoses may involve either malfunction of the sympathetic (adrenergic) mechanism or the para-sympathetic (cholinergic) or both, leading to significant departures from that reaction requisite for maximal mobilization of the organism. A hypothetical matrix of varieties of disordered responsiveness to stress has been constructed by reviewing the efficacy and mode of action of certain drugs already employed in the treatment and control of psychotic behavior with varying success. From the following evi-

[1] Department of Clinical Research, Eastern Pennsylvania Psychiatric Institute, Henry Avenue and Abbottsford Road, Philadelphia, Pennsylvania.

dence it has been deduced that disordered responsiveness to stress may be characterized by either an excessive or deficient adrenergic response mechanism.

Iproniazid (Marsilid) has been used extensively in the treatment of mental depression. *In vivo* studies with iproniazid on animals indicate that it can produce a relatively rapid and large (threefold) rise in brain serotonin (22). According to Truitt (21) it is likely that iproniazid, thru its inhibition of monoamine oxidase in the brain, potentiates the action therein of endogenous stimulant biogenic amines, possibly norepinephrine, epinephrine and serotonin. The implication here is that *some* psychotic patients who are benefited by iproniazid may be *defective* in some brain catechol amines or in central adrenergic stimulation.

When one turns to the treatment or control of the schizophrenic reaction, it is found that reserpine and chlorpromazine have been extensively used. Brodie and his associates have shown that the excretion of 5-hydroxyindoleacetic acid, a metabolite of serotonin, was markedly increased following the administration of reserpine (19). Furthermore, it was found (14) that the administration of reserpine markedly decreased the serotonin levels in the brain. As reserpine depletes the store of biogenic catechol amines in the brain, it is possible that in those instances in which reserpine therapy proves effective it may be due to the elimination of excessive concentrations of the biogenic amines in subcortical centers. The limited efficacy of reserpine therapy therefore suggests that *some* psychotic patients may be characterized by an *excessive* adrenergic activity in subcortical centers. This same conclusion is also applicable when chlorpromazine is considered. For in addition to its peripheral antihistaminic and anticholinergic effects, chlorpromazine has been shown to have an adrenergic blocking action.

In summary, it is postulated that the disordered responsiveness to stress which characterizes some psychotics may be due either to a neurohumoral deficiency of some sympathomimetic amine or to some enzyme disorder such as monoamine oxidase overactivity in the adrenergic excitatory mechanism of the brain; or, to a neurohumoral overabundance of some sympathomimetic amine or to some enzyme disorder such as monoamine oxidase underactivity in the adrenergic mechanism of the brain.

There are suggestions that the cholinergic component of generalized autonomic activity is also involved in the disordered responsiveness to stress which characterizes psychotic behavior. Forrer (5) has recommended the use of large doses of tertiary atropine in the treatment of manic-depressives in the manic phase. As the pharmacological action of atropine is that of a cholinergic blocking agent, it may be inferred that excessive brain acetylcholine or deficient acetylcholinesterase characterizes some psychotics. Hoffer (10) also has claimed that excessive para-sympathetic activity, with concomitant increases in the concentration of acetylcholine, is an essential feature of the schizophrenic process.

Pfeiffer *et al.* (12), on the other hand, have reported that some schizophrenic patients respond with a lucid interval to stimulation by cholinergic stimulants such as pilocarpine, arecoline and 2-dimethylamine ethanol. The implication of this report is that some psychotics are characterized by defective cholinergic responsiveness. Recently, Rubin (17, 18) measured the rate of hydrolysis of acetylcholine chloride by erythrocyte cholinesterase and found that some psychotics may be deficient in cholinergic activity while others may be characterized by excessive cholinergic activity.

A hurried review of the evidence presented may at first seem replete with paradoxical facts and theories. At first it appears that an effective chemotherapy for some psychotics should strive towards increasing central adrenergic activity. Then,

it seems that more effective drugs which decrease adrenergic activity should be developed. Additional conflict is raised by assertions of efficacy for cholinergic as well as anticholinergic drugs. These apparent contradictions may be resolved by viewing *the population of "functional psychotics" incapable of an organized normal response to stress as consisting of a specifiable number of discrete patterns of adrenergic-cholinergic levels of reactivity.* It is assumed that in the population of psychotics there may exist three levels of adrenergic activity, including overreactivity and deficiency of sympathetic outflow, as previously described, in addition to a normal level from which directional deviations are measurable. The cholinergic outflow may also be described as consisting of three levels; overreactivity or deficiency of cholinergic levels as measured by reference to a level characteristic of the unstressed normal. The matrix of autonomic steady states derivable from such a paradigm is presented in Figure 1. In this figure, "A" represents central adrenergic activity and "C," central cholinergic activity. The levels of activity of each dimension are symbolized by +, 0 and −. The positive sign represents excessive activity; the zero, normal activity; and, the negative sign, deficient activity. That level represented by (AoCo), Group V, characterizes the level of adrenergic and cholinergic activity in the unstressed normal individual. The eight other combinations represent hypothetical adrenergic-cholinergic levels of humans under stress. Previously, the hypothesis had been developed that a normal response to stress consists of maximal generalized sympathetic activity which is attained when cholinergic stimulation is decreased (C−) while adrenergic stimulation continues to increase (A+) up to that maximal level which characterizes the individual. This characteristic adjustment is represented in Figure 1, Group VII, and may be represented as A+C−. It is now further hypothesized within the framework of the general theory, that the remaining seven interactions represent the discrete patterns which comprise the population of "functional" psychotics.

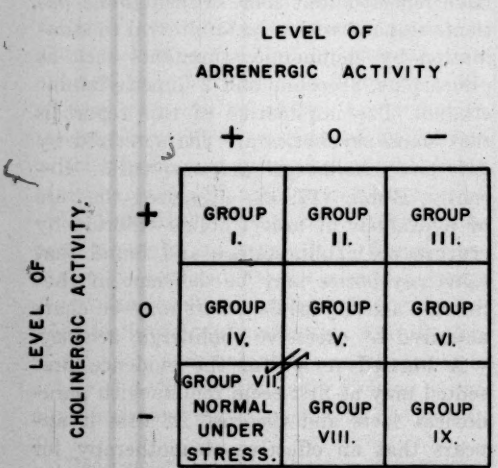


FIG. 1. Hypothetical patterns of adrenergic-cholinergic interaction for normals and psychotics.

To recapitulate, the major hypotheses tested in the experiment are: 1) effective adjustments to emergency situations require *maximal* generalized sympathetic response; 2) to attain a maximal level of sympathetic activity, it is not only necessary that increased levels of adrenergic activity follow the emergency but that the level of cholinergic activity decrease; 3) the disordered responses to stress which characterizes the functional psychoses represent significant departures from the adrenergic increase and cholinergic decrease which characterizes the effective, adjusting individual during stress; 4) the varieties of disordered response to stress represent discrete levels of activity of interacting adrenergic and cholinergic mechanism. That is, the disorder may represent an impairment of function of either the adrenergic or cholinergic mechanism, or both.

## METHOD

In order to test these hypotheses, a physiological measure of adrenergic and cho-

linergic activity was employed. The miotic response of the pupil to light and the mydriasis resulting in the absence of light were employed to measure cholinergic and adrenergic mechanisms respectively. The cholinergic nature of the activity of the oculomotor nerve under the influence of light has been proved by the positive assay for acetylcholine in the anterior chamber of the eye (3) and the disappearance of the light reflex after the injection of cholinesterase (11). Conversely, the anticholinesterases induce miosis. The work of Poos (15), Hess and Koella (8) and Hess *et al.* (9) on isolated radial preparations of the iris demonstrated contraction in response to small concentrations of adrenalin and noradrenalin. Since these substances are responsible for neurohumoral transmission in sympathetically innervated structures, they believe it is reasonable to assume that a dilator muscle exists which responds to sympathetic excitation. In addition, Frohlich and Loewi (6) had shown that the mydriasis induced by adrenalin is intensified by cocaine.

Since pupillary constriction had been shown to be dependent upon the liberation of acetylcholine and dilatation upon an adrenergic mediator, the present study employed measurements of rate of dilatation as representing the kinetics of a general adrenergic mechanism, and the rate of constriction as indicative of the kinetics of the cholinergic mechanism. To this end, measurements were made of the rate of dilatation of the pupil in darkness and the rate of constriction of the previously dark adapted pupil in the presence of light on normal subjects and psychotic patients.

### APPARATUS

The essential items of apparatus were a 35 mm camera with an attached 135 mm lens, bellows, and electronic flash which were employed to photograph the pupil. Three electronic timers accurate to 0.001 sec. were used for the automatic, systematic variation of the durations of exposure of the eye to a constant light intensity and to the absence of light. Each subject sat at a table with his head in a head-rest attached to which was a millimeter ruler which could be positioned in the same focal plane as the subject's right eye. The distance between the eye of the subject and the lens of the camera was 56.75 cm. and the distance between the eye and a fluorescent 2x2 mm fixation point mounted slightly below the lens was 65.6 cm. Attached to the camera tripod was a 75 W Mazda lamp which light-adapted the subject's eye at a constant luminance of 38.59 ft. candles. All measurements were made in a light-tight room.

### PROCEDURE

To obtain the rate of dilatation for each subject, the following procedure was employed. After the subject was seated with his head positioned in the head-rest, the room light was extinguished. After 5 secs. in the dark, the intense adapting light was focused on the subject's right eye for 10 secs. At the termination of this interval a photograph of the maximally constricted pupil was automatically taken. This was done twice, in an effort to equate for previous conditions of adaptation of the retina. Each subsequent photograph of the pupil was taken after the subject had been dark-adapted for a prescribed interval of time following maximal constriction. The intervals of dark adaptation employed were 5, 10, 15, 30, 45 and 60 seconds.

The procedure employed to obtain measurements of the rate of pupillary constriction was initiated soon after measurements of pupillary dilatation had been obtained. Each photograph of the pupil was taken after the subject had been light-adapted for a specific interval of time following maximal dilatation. The intervals of light adaptation employed were 1, 2, 3, 4 and 5 secs. Prior to obtaining a measurement of constriction at each of these intervals, the eye was light adapted for 10 secs. at a con-

stant intensity before it was permitted to dilate maximally within the 60 sec. dark adaptation period.

## EXPERIMENT 1

To test the hypothesis that normal subjects react to emergencies with an increased adrenergic response and a decreased cholinergic response, the following procedure was employed after control measurements of dilatation and constriction had been made on each of 15 normal subjects. Due to the variety of patterns of perceptual response that are elicited in humans to the "same" but variously interpreted environmental stimulus, it is difficult to define a stimulus situation that is realizable in a laboratory as an "emergency" or as "threatening." Consequently, the following procedure was used to elicit a physiological "stress" response. The right hand of the subject was immersed to above the wrist in a cold water bath maintained at 5°C.

### SUBJECTS

Control measurements of pupillary dilatation and constriction were obtained on eight white females and seven white males, between the ages of 19–40. This sample included secretaries, maintenance personnel, research technicians and professional persons employed at the Eastern Pennsylvania Psychiatric Institute. Six control subjects were then selected at random from the sample of 15 for a determination of the effect of the cold pressor test on pupillary dilatation and constriction.

### METHOD

Each of the six control subjects exposed to the cold pressor test participated in this phase of the experiment by immersing the hand in the cold water bath for five minutes while systolic and diastolic blood pressure measurements were obtained prior to determinations of pupillary reactivity. This was done in order to ascertain whether the physiological responsiveness of the subject would perseverate throughout an interval of time required to obtain measurements of either dilatation or constriction. The average increase in systolic B.P. was 11.0 mm Hg. and the average increase in diastolic B.P. was 15.3 mm Hg. At the end of five minutes the subject removed his hand from the cold water bath and rested for approximately 20 minutes to allow the systolic and diastolic pressures to return to the basal level as determined by measurement.

The subject was then required to sit with his chin in the head rest, his eyes focused on the fixation point and at a signal the right hand was immersed into a cold water bath. The procedure for determining the rate of pupillary dilatation as a function of time was then begun. On completion of the last measurement, the subject removed his hand from the bath and relaxed for another twenty minutes while the hand was warmed and diastolic/systolic blood pressures returned to the basal level. The subject was then prepared for measurements of pupillary constriction under the cold pressor condition. At the signal, the right hand was immersed in the water bath and measurements of pupillary constriction were begun.

### RESULTS

#### DILATATION

The average pupil diameter at each interval in darkness, *i.e.* 5, 10, 15, 30, 45 and 60 secs. for the six subjects under the control and cold pressor conditions is presented in Figure 2. Alexander's test for trend (2) was then applied to the raw data in order to determine whether the group means and group slopes differed significantly. The results of the analysis are presented under the column headed Dilatation in Table 1. The statistical analysis indicates that although there were significant differences between the slopes of individuals within groups, the difference between group slopes was not significant. Coupled with the finding of a significant difference, $p < .01$, between group

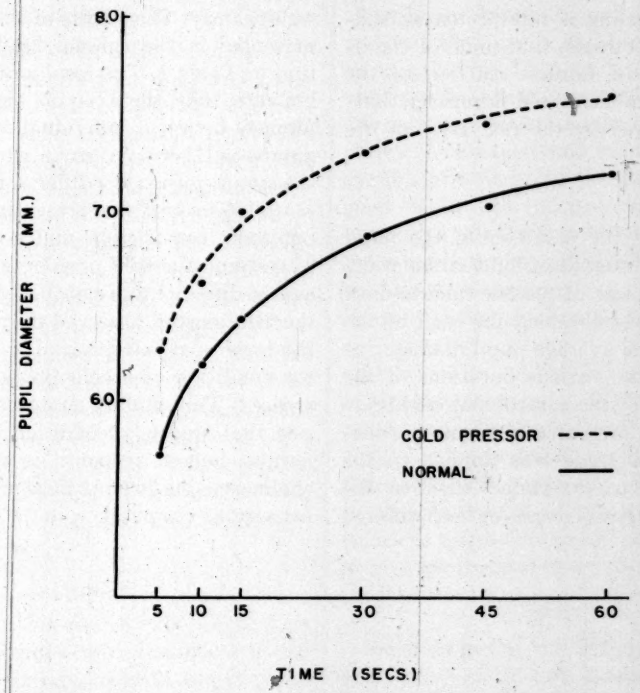


FIG. 2. Pupillary dilatation in normal subjects exposed to the cold pressor test.

TABLE 1

*Alexander's Trend Test Applied to Determine the Effect of the Cold Pressor Test on Pupillary Dilation and Constriction in Healthy People*

| Source of Variation | Dilatation | | | | Constriction | | | |
|---|---|---|---|---|---|---|---|---|
| | DF | M.S. | F | $p$ | DF | M.S. | F | $p$ |
| Between Group Means | 1 | 4.00 | 133.3 | <0.01 | 1 | 1.81 | 86.3 | <0.01 |
| Between Group Slopes | 1 | 0.03 | 1.0 | — | 1 | 0.001 | — | — |
| Group Deviations from Estimation | 4 | 0.01 | — | — | 3 | 0.06 | 2.8 | — |
| Between Individual Means | 10 | 2.12 | 70.6 | <0.01 | 10 | 0.47 | 22.5 | <0.01 |
| Between Individual Slopes | 10 | 0.11 | 3.7 | <0.01 | 10 | 0.03 | 1.5 | — |
| Over-all Deviations from Linearity | 4 | 0.13 | 4.3 | <0.01 | 3 | 0.73 | 34.5 | <0.01 |
| Over-all Slopes | 1 | 16.01 | 533.7 | <0.01 | 1 | 5.11 | 243.3 | <0.01 |
| Individual Deviations from Estimation (error) | 40 | 0.03 | | | 30 | 0.02 | | |

means, it is concluded that the curves under the control and pressor condition are significantly different and parallel. The rate of pupillary dilatation under these conditions is presented in Figure 2, in which the slopes are presented as approximately equal and parallel while the absolute level of dilatation under the condition of the cold pressor test is seen to be greater. The cold pressor test increased pupillary dilatation signifi-

cantly. This finding is interpreted as supporting the hypothesis, that under a condition of stress the normal reaction of the human is for an increased adrenergic outflow, as measured by the reactivity of the pupil.

CONSTRICTION

The value of the diameter of the pupil following each interval of light stimulation, *i.e.* 1, 2, 3, 4, 5 sec., of the one minute dark adapted eye, was obtained for each of the six subjects. The average pupil diameter as a function of the various durations of the light stimulus for the control and cold pressor condition is presented in Figure 3. Alexander's test for trend was applied to the data in order to determine whether the group slopes or group means or both differed significantly. The results of the analysis are presented in the column headed Constriction in Table 1. The results of the analysis indicate that there is no significant difference between individual slopes within groups nor between group slopes, but that the group means do differ significantly ($p < .01$). The curves representing the rate of pupillary constriction under the condition of rest and the cold pressor test are significantly different and parallel. As opposed to the relationship observed during dilatation, the level of constriction of the pupil under the condition of a cold pressor test, is *decreased*. This finding supports the hypothesis that under a condition of stress the normal human response is a decrease in cholinergic outflow, as measured by the reactivity of the pupil.

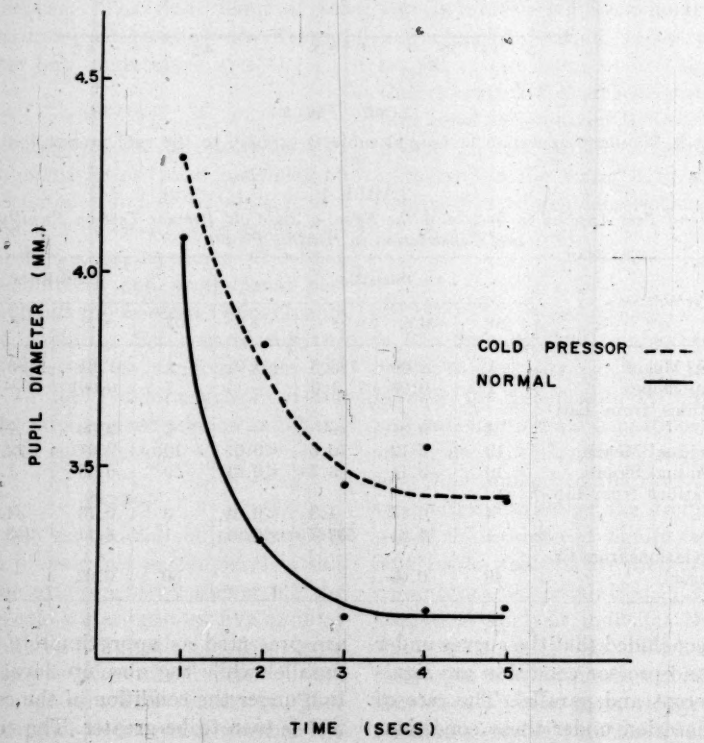


FIG. 3. Pupillary constriction in normal subjects exposed to the cold pressor test.

## EXPERIMENT 2

This experiment was designed to test two additional hypotheses that were previously described: the disordered responses to stress which characterize functional psychoses represent significant departures from the adrenergic increase and cholinergic decrease which characterizes the effective individual during stress; and, the varieties of disordered response to stress represent discrete predictable patterns of interaction of the adrenergic-cholinergic mechanisms.

It may be recalled that these patterns were hypothesized after a review of pharmacological evidence which suggested to the author that there was a possibility of three levels of adrenergic activity and three levels of cholinergic activity. Of the total of nine patterns thus derived, the first experiment characterized two.

### SUBJECTS

The data in this second experiment were obtained from nine control subjects in addition to the six employed in the previous experiment. Of the total of 15 control subjects, between the ages of 19–40, there were eight females and seven males. All subjects were necessarily Caucasian because of the difficulty encountered in photographing and measuring the heavily pigmented irides of Negroes. This sample included secretaries, maintenance personnel, research technicians and professional persons employed at the Eastern Pennsylvania Psychiatric Institute.

Twenty-four patients, 13 white males and 11 white females between the ages of 15–42, clinically diagnosed as functionally psychotic by the psychiatric staff, were employed. This sample comprised ten paranoid schizophrenic patients of which two had schizo-affective features; six acute schizophrenic reactions; four chronic undifferentiated schizophrenics; three catatonics; and one involutional psychotic reaction. Sixteen of the twenty-four patients had been receiving some form of psychotherapy, four had received chemotherapy (thorazine) while in the Institute, and of five who had received EST, three had been discontinued on this therapy from six to 12 months previous to the experiment and two had been discontinued several weeks prior to the experiment. Medical and routine laboratory examination revealed the patients to be in good health. No patient was reported as presenting any feeding problem. Forty-eight hours prior to the taking of measurements, the thorazine regimen was discontinued for the four patients under this treatment.

### METHOD

Measurements of pupillary dilatation and constriction were obtained on 15 normal control subjects and 24 patients, employing the procedures previously described. Each patient was tested on two consecutive days to insure a complete record of measurements at all experimental intervals.

### RESULTS

Whereas in the first experiment each subject served as his own control in determining the effect of a stress-engendering situation, this procedure obviously could not be employed in the experiment being described. Instead, determinations of patterns of disordered cholinergic-adrenergic activity characteristic of the functional psychoses were made relative to patterns shown by the normal controls.

#### DILATATION

The diameter of the pupil following each interval of darkness, *i.e.* 5, 10, 15, 30, 45 and 60 secs., was obtained for each control subject and patient. Then, in order to determine the extent of dilatation between the fifth and sixtieth seconds, independent of individual differences in the final level of dilatation attained, the following measurement was employed. The initial level of dilatation (mm.) was subtracted from the final level of dilatation (mm.) and divided by the final level of dilatation. The ratio obtained for each control subject and each

TABLE 2

*The Extent of Pupillary Dilatation* and Constriction† in Normals and Psychotics*

| Normals | | | Patients | | |
|---|---|---|---|---|---|
| Subject | Dilatation | Constriction | Subject | Dilatation | Constriction |
| 1 | 0.154 | 0.305 | 1 | ←0.114 | 0.382 |
| 2 | 0.182 | 0.292 | 2 | 0.292→ | 0.786→ |
| 3 | 0.171 | 0.181 | 3 | ←0.129 | 0.158 |
| 4 | 0.216 | 0.275 | 4 | 0.254→ | 0.643→ |
| 5 | 0.242 | 0.408 | 5 | 0.204 | 0.562→ |
| 6 | 0.187 | 0.393 | 6 | 0.267→ | 0.433→ |
| 7 | 0.207 | 0.213 | 7 | ←0.125 | 0.363 |
| 8 | 0.205 | 0.234 | 8 | 0.253→ | 0.316 |
| 9 | 0.165 | 0.376 | 9 | ←0.137 | 0.350 |
| 10 | 0.208 | 0.259 | 10 | 0.210 | ←0.111 |
| 11 | 0.181 | 0.234 | 11 | ←0.105 | 0.211 |
| 12 | 0.229 | 0.322 | 12 | 0.200 | 0.473→ |
| 13 | 0.203 | 0.251 | 13 | 0.226 | 0.602→ |
| 14 | 0.226 | 0.222 | 14 | ←0.083 | 0.904→ |
| 15 | 0.226 | 0.333 | 15 | 0.235 | 0.531→ |
| | | | 16 | 0.297→ | 0.522→ |
| | | | 17 | 0.167 | 0.648→ |
| Range: | (0.154–0.242) | (0.181–0.408) | 18 | 0.196 | 0.615→ |
| | | | 19 | 0.183 | ←0.140 |
| Mean: | 0.200 | 0.287 | 20 | ←0.145 | ←0.131 |
| | | | 21 | 0.225 | 0.933→ |
| | | | 22 | 0.226 | 0.442→ |
| Standard Deviation(s) | 0.0258 | 0.0687 | 23 | 0.208 | 0.438→ |
| | | | 24 | ←0.082 | 0.606→ |

* Extent of Dilatation = Final Level (m.m.)—Initial level (m.m.)/Final level (m.m.)

† Extent of Constriction = Initial level (m.m.)—Final level (m.m.)/Final level (m.m.)

patient is presented in Table 2, together with the mean and the range of values obtained for the control subjects. Assuming that the sample of healthy subjects employed in the experiment is a random sample from a population with a normal distribution for the obtained ratio, then the sample mean, as an unbiased estimate of the population mean, may be employed to determine the likelihood of obtaining values for the ratio which deviate significantly in the direction of excessive or deficient dilatation. The probability of obtaining a ratio equal to or greater than 0.250 was found to be $p \leqslant .025$, and of obtaining a ratio equal to or less than 0.150, $p \leqslant .025$. Values of the ratio for the patients which fall beyond the interval 0.250–0.150 have been marked with an arrow. The direction of the arrow indicates whether the value of the ratio is significantly less than (←) the lowest probable value within the normal range or greater than (→) the highest probable value within the normal range for dilatation. Those ratios which are unmarked all fall within the limits for normal values. The average value for those subjects who demonstrated less dilatation than the normals was obtained, as was the average value for those subjects who demonstrated greater dilatation. The significance of the difference between each of these groups and mean value of the control subjects was determined by means of the t-test. The results of this analysis are presented in Table 3. The mean value of the groups of patients that were categorized on a basis relative to the probability limits of normal values for the extent of dilatation are, as expected, significantly different from the mean value of the control group, with $p < .01$ for each comparison. The results therefore indicate that the members of the patient group fall into any one of three discrete groups with respect to extent of dilatation. One group shows the same extent of dilatation as the normal controls (11/24); another group shows excessive dilatation (5/24); and the third group demonstrates deficient dilatation (8/24). These relationships are graphically presented in Figure 4. In this figure the values of the ordinate consist of the

TABLE 3

*A Comparison Between the Controls and Patients with Respect to the Extent of Dilatation and Constriction*

| | Dilatation | | | Constriction | | |
|---|---|---|---|---|---|---|
| | Patients | | Control | Patients | | Control |
| | Defective | Excessive | | Defective | Excessive | |
| Mean | 0.115 | 0.272 | 0.200 | 0.127 | 0.609 | 0.287 |
| n | 8 | 5 | 15 | 3 | 15 | 15 |
| t | 8.02 | 5.58 | | 3.92 | 7.28 | |
| $p$ | <0.01 | <0.01 | | <0.01 | <0.01 | |

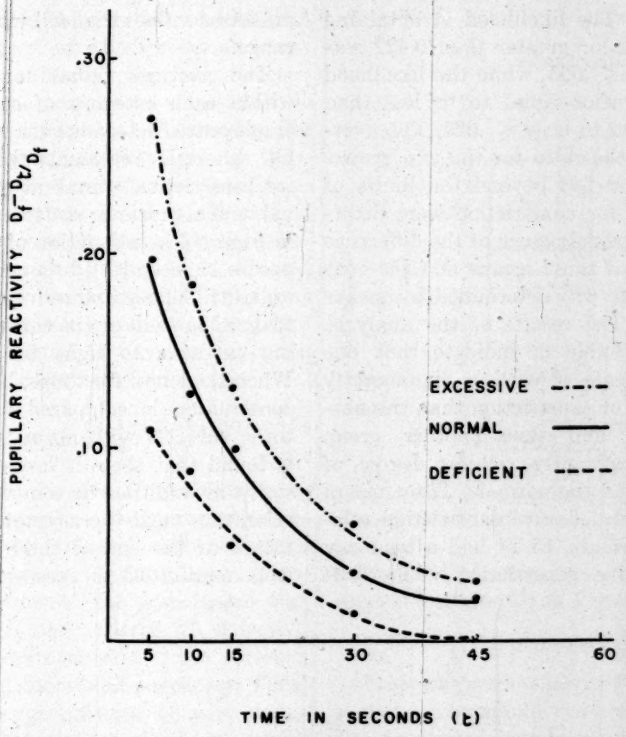


FIG. 4. Reactivity levels of pupillary dilatation in psychotic patients.

final level of dilatation ($D_f$), the extent of dilatation after 60 seconds, minus the level of dilatation after each interval of darkness ($D_t$) divided by the final level of dilatation ($D_f$), $D_f - D_t/D_t$, and the abscissa represents the intervals of darkness in seconds, t, preceding photographs of the pupil. To calculate the ratio, the mean values for each interval were employed. It is clear that three levels of dilatation appear to characterize the sample of patients in the experiment. The hypothesized three distinct levels of adrenergic activity, as measured by pupillary reactivity, seem to have been confirmed.

CONSTRICTION

The diameter of the 1 min. dark adapted pupil of the eye, was obtained following exposure to a constant intensity which lasted for 1, 2, 3, 4 or 5 secs. These values were obtained for each control subject and patient. In order to determine the extent of constriction of the pupil of the dark-adapted eye between the first and fifth seconds, independent of individual differences in final level attainable, a derived measure was used for each subject. To avoid negative values, the final level of constriction (mm.) was subtracted from the invariably greater initial level (mm.) and then divided by the final level. The ratio thus obtained for each control and patient is presented in Table 2, together with the mean and the range of values obtained for the control subjects. Arrows have again been employed to designate whether the value of the ratio for each patient is less than or greater than the calculated limits of the ratio between which 95 per cent of the values may be ex-

pected to fall. The likelihood of obtaining values equal to or greater than 0.422 was found to be $p \leqslant .025$, while the likelihood of obtaining ratios equal to or less than 0.152 was found to be $p \leqslant .025$. The average values of the ratio for the two groups of patients who fell beyond the limits of normal values for constriction were determined, and the significance of the difference between each of these means and the control mean value was determined by means of the t-test. The results of the analysis, presented in Table 3, indicate that one group of patients showed a significantly greater degree of constriction than the normal subjects, and that another group showed a significantly smaller degree of constriction than the normals. Three out of 24 patients had defective constriction relative to the normals, 15/24 had a tendency toward excessive constriction while 6/24 possessed values that fell within the normal range.

The average values for each interval within each category of constriction were employed to determine the ratio, $D_t - D_t / D_t$, where $D_t$ represents the average value for constriction (mm.) at each time interval, t. This ratio is plotted on the ordinate in Figure 5 as a function of duration of exposure in seconds, t, to a constant intensity of light. The asymptote for constriction was realized in each of the three groups following exposure to light for three seconds. When the curve for those showing defective constriction is compared to the curve of those subjects with normal constriction, it is found that there is less constriction initially in addition to somewhat slower deceleration until the asymptotic level is attained at the end of three seconds. Those who manifested an excessive tendency to-

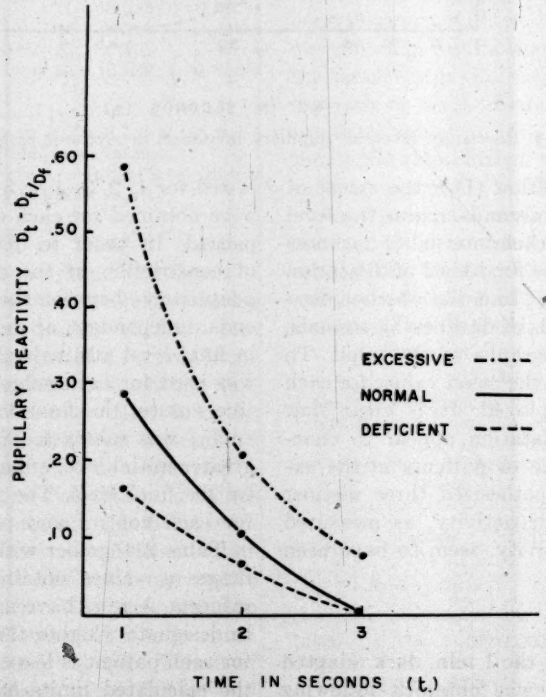


FIG. 5. Reactivity levels of pupillary constriction in psychotic patients.

ward constriction, as a group, started with a very high level of constriction and proceeded at approximately the same decelerating rate as the normals to an asymptotic level at three seconds which remained higher than the normal and defective groups. With respect to constriction, three levels of constrictive tendency are found in the sample of patients employed in this study; approximately 25 per cent of the patients showed no impairment in constriction, 12.5 per cent showed retardation in constriction, and 62.5 per cent were found to have an excessive tendency towards constriction.

### THE INTERACTION OF DILATATION AND CONSTRICTION

The results of the preceding sections confirmed initial hypotheses concerning the varieties of levels of adrenergic and cholinergic activity as measured by pupillary reactivity. An extension of the hypotheses was concerned with the matrix of defective steady-states characteristic of the varieties of the so-called functional psychoses. Thus, in Figure 1, seven patterns of adrenergic-cholinergic interaction, each characteristic of a discrete disordered stress state, were described. The demonstration of these patterns of interaction is derivable from the following considerations.

Eleven out of twenty-four psychotic patients showed no impairment in the extent of dilatation (Table 2). However, *all* of the members in this group manifested *aberrant* constriction. Nine out of the eleven manifested excessive constriction, while two were deficient. Conversely, of the six patients out of the twenty-four who showed no impairment in constriction, *all* were aberrant in the extent of dilatation; five had less dilatory tendency and one had more than the controls. Or, in confirmation of the hypothesis it may be stated that all twenty-four patients in the study showed a significant impairment in either the tendency to dilatation or to constriction or both. A frequency distribution of these patterns of interaction of adrenergic-cholinergic mechanisms is presented in Figure 6.

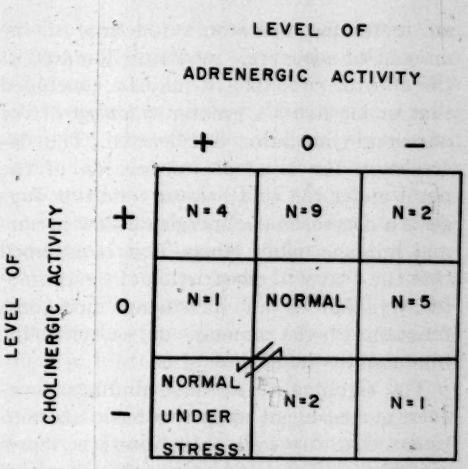


FIG. 6. A frequency distribution of the patterns of interaction of adrenergic-cholinergic mechanisms in a sample of psychotic patients.

### DISCUSSION

Accepting a view held by many and supported by numerous research findings, that the functional psychoses represent a disordered response to stress, a theoretical framework was developed which was tested in a preliminary way in this report. The accepted role of the sympathicoadrenal system in response to emergency situations was extended to include the role of cholinergic mechanisms. The specific hypotheses were confirmed that the characteristic reaction of the autonomic nervous system to stress in normal individuals consisted of increased sympathetic (adrenergic) activity and decreased para-sympathetic (cholinergic) activity, as measured by pupillary reactivity.

The finding that the cold pressor test increased pupillary dilatation significantly is interpreted as supporting the hypothesis that under a condition of stress, the normal human reaction is for an increased adrenergic outflow. That is, assuming that the responsiveness of the dilator pupillae is

an increasing monotonic function of the amount of adrenergic mediator liberated at the effector site, then it may be concluded that under stress a greater quantity of the adrenergic mediator is liberated. The decrease in the level of constriction of the pupil under the cold pressor condition suggests a decreased cholinergic outflow in normal humans under stress, if it is assumed that the degree of constriction of the sphincter pupillae is an increasing monotonic function of the amount of acetylcholine liberated at the effector sites.

The significance of these findings, however, is contingent upon two basic assumptions: that the cold pressor test is representative and equivalent to other forms of physiological or psychological stress and that the adrenergic and cholinergic reactivity of the pupil is representative of adrenergic-cholinergic mechanisms of interaction in vital neural integrative centers such as the posterior and anterior regions of the hypothalamus respectively. If these assumptions are accepted, the following interpretation of the results of the experiment may be made with reasonable assurance. When the normal human organism is exposed to a stress-engendering situation, autonomic mechanisms respond with an increased sympathetic (adrenergic) outflow and a decrement in para-sympathetic (cholinergic) outflow. This reciprocal balance between the components insures maximal mobilization of the resources of the organism required for "fight, flight, or fright."

In support of the hypothesis that the functional psychoses may be characterized by disordered responses to stress (which deviate significantly from the adrenergic increase and cholinergic decrease of the normal subject under stress), it was first shown that the psychotic sample manifested three distinct levels of dilatation and three significantly different levels of constriction. Again, if it is assumed that the magnitude of pupillary dilatation is proportional to the quantity of adrenergic mediator liberated, then it may be concluded that some of the patients liberated a quantity which was characteristic of normals at rest; others, liberated more of the adrenergic mediator or had some enzyme disorder such as monoamine oxidase underactivity; and some liberated too little of the adrenergic mediator or had some enzyme disorder such as overactivity of monoamine oxidase. Assuming that the tendency toward constriction of the sphincter pupillae is proportional to the quantity of acetylcholine liberated, the demonstration of three levels of constriction suggests that in more than half the patients either excessive quantities of acetylcholine were liberated or that there was deficient acetylcholinesterase activity; in some patients insufficient quantities of the neurohumor were liberated or else enzyme activity was excessive. The cholinergic activity of some patients was equivalent to the level of normal subjects.

Those patients who showed no impairment in the extent of dilatation all demonstrated impairment in the rate of constriction; those patients who showed normal constriction all manifested impairment in dilatation. These findings confirmed the hypothesis that the disordered responses to stress in functional psychoses represent significant departures from the adrenergic increase and cholinergic decrease of the effective, adjusting individual during stress.

That the functional psychotic may be classified into discrete categories of adrenergic-cholinergic levels of activity throws reasonable doubt upon the current quest for a single chemical panacea. Instead, the results of this study suggest that each pattern of adrenergic-cholinergic activity may require a specific combination of drugs which differentially effect the level of activity of either or both components of the autonomic nervous system. This assumes, of course, that the underlying biochemical defect is in fact reversible. While

adrenergic and adrenolytic drugs and cholinergic stimulants and cholinergic blocking agents have been employed in clinical chemotherapeutic trials with limited success, it should be noted that administration of these drugs is generally not selective. Usually, a behavioral evaluation is made of a sample of patients presumed to be representative of a homogeneous population of psychotics before and after a specific drug is administered. The value of the present study is that it seems to provide a rationale for the selection of patients who require distinct chemotherapies as determined by the specific pattern of adrenergic-cholinergic imbalance.

Although little has been written about the aim of chemotherapy, most workers in the area would agree that it is not expected that alleviation of a presumably reversible biochemical disorder would automatically restore the disturbed individual to a normal state. Rather, following the reestablishment of a "normal" biochemistry, the maladaptive responses acquired during the course of the illness would have to be restructured. As the normal individual was found to possess two "normal" patterns of adrenergic-cholinergic interaction, one while at rest and the other under stress, it may be important to consider the efficacy of retraining as a function of these patterns of interaction.

## SUMMARY

Measurements of pupillary reactivity were employed to test hypotheses deduced from a general theory of the interaction of adrenergic and cholinergic mechanisms in psychiatric disorders. Accepting the requirement of a maximal generalized sympathetic response for effective adjustment to emergency or threatening situations, it was then shown that an adequate response to stress consisted of an increased adrenergic outflow and a concomitant decrease in the level of cholinergic activity. The disordered responses to stress which characterize the functional psychoses were demonstrated to represent significant departures from the adrenergic increase and cholinergic decrease typifying the effective, normally adjusting individual during stress. The experiments confirmed the existence of specific patterns of discrete adrenergic-cholinergic interaction that significantly differentiated psychiatric patients from normal, healthy people. The patterns of disordered responsiveness to stress demonstrated an impairment of function of either the adrenergic or cholinergic mechanism or both. It is suggested that the results of the experiments provide a rational basis for chemotherapy with the so-called functionally psychotic patient population

## REFERENCES

1. Adler, F. H. *Physiology of the Eye, Clinical Application*. 2nd ed. Mosby, St. Louis, 1953.
2. Alexander, H. W. A general test for trend. Psychol. Bull., **43**: 533–557, 1946.
3. Engelhart, E. Der humorale wirkungs-mechanismus der okulomotoriusreizung. Arch. ges. Physiol., **227**: 220–234, 1931.
4. Finkelman, I. and Stephens, W. M. Heat regulation in dementia praecox; reactions of patients with dementia praecox to cold. J. Neurol. & Psychopath., **16**: 321–340, 1936.
5. Forrer, G. R. Symposium on atropine toxicity therapy, history and future research. J. Nerv. & Ment. Dis., **124**: 256–259, 1956.
6. Fröhlich, A. and Loewi, O. Über eine steigerung der adrenalin empfindlichkeit durch cocain. Arch. exper. Path. u. Pharmakol., **62**: 159–169, 1910.
7. Fulton, J. F. *A Textbook of Physiology*. 16th ed. Saunders, Philadelphia, 1949.
8. Hess, W. R. and Koella, W. Experimentelle studien über die antagonistische innervation. Ztschr. ges. exper. Med., **116**: 431–443, 1950.
9. Hess, W. R., Koella, W. and Szabo, T. Experimentelle studien über die antagonistische innervation. Ztschr. ges. exper. Med., **115**: 481–490, 1950.
10. Hoffer, A. Epinephrine derivatives as potential schizophrenic factors. J. Clin. & Exper. Psychopath., **18**: 27–60, 1957.
11. Mendel, B. and Hawkins, R. D. Removal of acetylcholine by cholinesterase injections and effect thereof on nerve impulse transmission. J. Neurophysiol., **6**: 431–438, 1943.
12. Pfeiffer, C. C., Jenney, E. H., Gallagher, W., Smith, R. P., Bevan, W., Killam, K. F., Kil-

LAM, E. E. AND BLACKMORE, W. Stimulant effect of 2-dimethyl aminoethanol. Science, **126**: 610–611, 1957.

13. PFISTER, H. D. Disturbances of autonomic nervous system in schizophrenia and their relations to insulin cardiazol and sleep treatments. Am. J. Psychiat., **94**: 109–118, 1938.
14. PLETSCHER, A. P., SHORE, A. AND BRODIE, B. B. Serotonin as a mediator of reserpine action in brain. J. Pharmacol. & Exper. Therap., **116**: 84–89, 1956.
15. Poos, F. Über die eignung der pupillae als testobjekt fur pharmacologische reaktionen und pharmakodiagnostik an auge. Ergebn. Physiol., **41**: 883–916, 1939.
16. RICHTER, D., ed. *Schizophrenia: Somatic Aspects*. Macmillan, New York, 1957.
17. RUBIN, L. S. Acetylcholine hydrolysis in psychiatric patients. Science, **128**: 254–255, 1958.
18. RUBIN, L. S. Cholinesterase activity. Science, **128**: 1176–1178, 1958.
19. SHORE, P. A., SILVER, S. L. AND BRODIE, B. B. Interaction of reserpine, serotonin and lysergic acid diethylamide in the brain. Science, **122**: 284–285, 1955.
20. SYMTHIES, J. R. The biochemistry of schizophrenia. Lancet, **2**: 308–313, 1958.
21. TRUITT, E. B. Some pharmacologic correlations of the chemotherapy of mental disease. J. Nerv. & Ment. Dis., **216**: 184–210, 1958.
22. ZELLER, E. A., BARSKY, J. AND BERMAN, E. R. Amine oxidases inhibition of monoamine oxidase by l-isonicotinyl-2-isopropylhydrazine. J. Biol. Chem., **214**: 267–274, 1955.

# OBSERVATIONS ON FORTY TWIN INDEX CASES WITH CHRONIC EPILEPSY AND THEIR CO-TWINS[1]

EIJI INOUYE, M.D.[2]

## INTRODUCTION

Extensive studies on epileptic twins by Lennox (18, 19) and Lennox and Jolly (20) have dealt with both genetic and environmental factors not only in the etiology of epilepsy, but also in the formation of its symptoms. They confirmed a higher concordance of epilepsy in monozygotic (MZ) twins than in dizygotic (DZ) twins, a finding reported in earlier studies by Rosanoff, Handy and Rosanoff (21) and Conrad (2–4). Lennox and Lennox *et al.*, however, did not fully deal with complex inter-relation of heredity and environment involved in the etiology of epilepsy. Detailed analysis of histories and symptoms of MZ twins by Conrad had suggested this possibility. Can MZ twins be classified into three groups with respect to similarity of symptoms, as Conrad has suggested? If so, there is the question as to what is the specific symptom of each group, and what are the environmental agencies causing intra-pair differences of the symptoms of epilepsy in MZ twins.

## METHODS

To begin to deal with such problems as those mentioned above, detailed examination of MZ twin index cases and their co-twins is clearly needed. This paper reports the results of a study of forty epileptic twins and co-twins. Twins who did not receive personal examination by the author or by collaborators, or had died before the examinations had been completed, were eliminated from the material. Twin index cases, which had experienced only transient convulsions or syncope in their infancy and showed no obvious clinical symptoms, could not be diagnosed accurately, and were also eliminated from the study.

Zygosity was diagnosed by the method established by Inouye (8, 9, 10), which employs blood groups (ABO, MN, P, in some cases C, c, D, E), salivary excretion type, finger prints and eighty-five items of anthropological traits, including ear wax, taste ability to phenylthiocarbamide and mid-digital-hair. Careful clinical examinations were completed: they included a psychiatric interview, neurological examination and psychological tests (including intelligence tests, Rorschach and other measures of personality). EEG examination was also routinely given, using eight monopolar leads (frontal, temporal, parietal and occipital leads of both sides). Records at rest, activated by hyperpnea and—in some cases—during sleep were obtained.

There were two primary sources of subjects. Twenty-three twin index cases were collected among out-patients and in-patients at the University of Tokyo Neuropsychiatric Clinic, where all patients were regularly asked whether or not they were twins. The remaining seventeen index cases are single cases reported by representative clinics, schools and other informants in all parts of Japan in reply to a circulated inquiry.

EEG records of seven MZ index cases or co-twins were not available, but all were diagnosed as epileptic with no difficulty. All but four pairs of MZ twins were repeatedly re-examined by the author and

[1] Preliminary reports on the majority of cases were made by Kamide and Fukuda (15, 16) and Kamide (17) in Japanese. The study was supported by Grants for Fundamental Scientific Research of Ministry of Education.

[2] Institute of Brain Research, University of Tokyo School of Medicine, Tokyo, Japan. The author acknowledges with thanks the collaborations of Drs. H. Kamide, T. Suzuki and T. Fukada.

his collaborators for a period ranging from one to nine years. Data on forty index cases with chronic epilepsy and their co-twins were then analyzed. One pair of twins, and one twin of another pair, died after examinations had almost been completed.

Detailed data on each MZ index case and co-twin were so obtained. It should be noted, however, that this method of subject selection does not guarantee an entirely unbiased sample.

## RESULTS

### ZYGOSITY

Of a total of forty pairs, twenty-six pairs were diagnosed as MZ, and fourteen pairs as DZ. There was no case of questionable zygosity.

A female MZ twin pair (Case 25) and a female DZ twin pair (Case 28) were born as triplets, one member of which was stillborn in each case. Thus the actual number of MZ twin pairs is twenty-five, and that of DZ twin pairs is thirteen. The observed numbers of twins and triplets do not significantly differ from expected numbers (Table 1), which were estimated from data on all twin and triplet births in Japan (11), since the frequency of triplets, one member of which is stillborn, is not known.

Observed numbers of two zygosities of twins do not differ significantly from expected numbers (Table 2), which were estimated from the ratio of MZ to DZ at birth, in cases where both twins are live born (11). There is only one pair of opposite-sexed DZ twins in this series, the shortage of which is, however, not significant (Table 2). There is also no excess of male or female twins in MZ pairs ($\chi^2 = 0.31$, $p > 0.50$) and in all twin pairs ($\chi^2 = 0.001$, $p > 0.95$).

The two surviving members of each triplet set are considered to be equivalent to other twin pairs in their respective series, and have been so treated in the analyses.

TABLE 1
*Observed and Expected Numbers of Twin Pairs and Triplet Sets*

| | Twins | Triplets | Total |
|---|---|---|---|
| Observed | 38 | 2 | 40 |
| Expected* | 39.77 | 0.23 | 40.00 |
| Total | 77.77 | 2.23 | 80.00 |

$\chi^2$(Yates) = 0.27, $p > .50$.
* twin birth:triplet birth = 520:3 (11).

TABLE 2
*Observed and Expected Numbers of Twin Pairs*

| | MZ | DZ | Total |
|---|---|---|---|
| Observed | 25 | 13 | 38 |
| Expected* | 24.57 | 13.43 | 38.00 |
| Total | 49.57 | 26.43 | 76.00 |

$\chi^2$(Yates) = 0.01, $p > .90$.

| | Same-sexed | Opposite-sexed | Total |
|---|---|---|---|
| Observed | 37 | 1 | 38 |
| Expected* | 31.29 | 6.71 | 38.00 |
| Total | 68.29 | 7.71 | 76.00 |

$\chi^2$(Yates) = 3.20, $p > .05$.
* MZ:DZ = 1.83:1, if both twins are live born (11).

### CLINICAL SYMPTOMS

A brief survey of types of seizures, age of onset and major EEG paroxysmal dysrhythmia of twin index cases and co-twins is shown in Tables 3–6. Clinical seizures were classified into three convulsive types (grand mal, focal and Jacksonian), three petit mal types (absence, akinetic and myoclonic), psychic seizures and febrile seizures. Psychic seizures involving psychomotor, automatism and "epileptischer Dämmerzustand" were not classified into subtypes, since to establish the indisputable subtype is often difficult. Reliable information on febrile seizures and whether they had been generalized, focal, Jacksonian or petit mal, was usually not available, and these seizures were also not classified. Autonomic seizures were occasionally accompanied by other types of seizures, but there is no case of autonomic seizures alone, and this tabulation was unnecessary.

TABLE 3

*Survey of Clinical Data: Concordant MZ Pairs with Marked Intra-pair Similarity*

| Case | Age under Observation | Clinical Type of Seizures (Age of Onset) | EEG Dysrhythmia |
|---|---|---|---|
| (Male = Male) | | | |
| 1. twin | 34–41 | febrile seizure (3m) grand mal (14) | borderline abnormalities |
| co-twin | 34–41 | febrile seizure (3m) grand mal (13) | borderline abnormalities |
| 2. twin | 23–27 | febrile seizure (8m) grand mal (?) | slow burst, spike, spike-wave |
| co-twin | 23–27 | febrile seizure (6m) grand mal (?) | slow burst, spike, spike-wave |
| 3. twin | 18–24 | grand mal (12) | slow burst, spike, spike-wave |
| co-twin | 18–24 | grand mal (12) | slow burst, spike, spike-wave |
| 4. twin | 17–19 | grand mal (9) | spike, spike-wave |
| co-twin | 17–19 | grand mal (8) psychic (17) | spike, spike-wave |
| 5. twin | 16–18 | grand mal (12) psychic (16) | ? |
| co-twin | 16–18 | grand mal (13) | ? |
| (Female = Female) | | | |
| 6. twin | 15–20 | febrile seizure (3m) grand mal (12) | spike |
| co-twin | 15–20 | febrile seizure (3m) grand mal (13) | spike |
| 7. twin | 12–19 | grand mal (8) | slow burst, spike |
| co-twin | 12–19 | grand mal (8) | slow burst, spike, spike-wave |
| 8. twin | 7 | absence (2) | spike-wave |
| co-twin | 7 | absence (2) | spike-wave |

### CONCORDANCE AND DISCORDANCE OF EPILEPSY (TABLE 7)

Of twenty-six MZ pairs, fourteen (54 per cent) are concordant with respect to clinical onset of seizures, while one pair of the fourteen DZ pairs is so concordant. The difference between these two rates of concordance is highly significant ($p$ (Fisher) $< 0.01$). As shown in Table 4 and Table 6, definite EEG dysrhythmia was found in six MZ and one DZ clinically normal co-twins. Concordant ratio of epilepsy with respect to clinical onset of seizures or EEG dysrhythmia in MZ twins thus becomes 77 per cent, and that in DZ twins 22 per cent. This difference is again highly significant ($p < 0.01$).

These results were compared with those reported by earlier investigators. Concordant ratios reported by Rosanoff *et al.* were corrected, since their figures had been based upon concordance, even when a given co-twin had suffered from a disease of other diagnostic category. The data of Lennox *et al.* were also corrected since their figures were based upon numbers of MZ and DZ pairs, in which twins suffering from transient seizures were included. The result of the present study confirms the important role of heredity in the etiology of epilepsy. At the same time the presence of MZ twins discordant in clinical onset of seizures as well as in EEG dysrhythmia confirms the presence of an environmental factor.

If a disease or a syndrome is etiologically heterogeneous, and if both genetic and environmental factors contribute to the etiology, one would expect to find hereditary cases among concordant MZ index cases and co-twins, and to find non-hereditary cases among discordant MZ index cases. If there is a case in which both factors are etiologically important, one would expect to find it

TABLE 4

*Survey of Clinical Data: Concordant MZ Pairs with Marked Intra-pair Dissimilarity*

| Case | Age under Observation | Clinical Type of Seizures (Age of Onset) | EEG Dysrhythmia |
|---|---|---|---|
| (Male = Male) | | | |
| 9. twin | 79–80 | Jacksonian* | ? |
| co-twin | 79–86 | none* | spike |
| 10. twin | 22–30 | grand mal (12) absence (18) | borderline abnormalities |
| co-twin | 22–30 | psychic (12) grand mal (17) | borderline abnormalities |
| 11. twin | 19–28 | psychic (11) grand mal (14) | slow burst, spike-wave |
| co-twin | 19–28 | psychic (12) grand mal (20) | slow burst |
| 12. twin | 12–18 | febrile seizure (2) grand mal (10) | slow burst, spike, spike-wave |
| co-twin | 12–18 | febrile seizure (2) | spike, spike-wave |
| 13. twin | 10 | Jacksonian (8) | ? |
| co-twin | 10 | grand mal (7) | ? |
| 14. twin | 5–8 | febrile seizure (1) Jacksonian (3) | slow burst, spike, spike-wave |
| co-twin | 5–8 | febrile seizure (1) | slow burst |
| (Female = Female) | | | |
| 15. twin | 27 | grand mal (14) psychic (?) | slow burst, spike, spike-wave |
| co-twin | 27 | none | slow burst, spike |
| 16. twin | 18–26 | Jacksonian (2) | slow burst, spike |
| co-twin | 18–26 | none | slow burst, spike |
| 17. twin | 15–22 | febrile seizure (1) grand mal (14) | slow burst, spike |
| co-twin | 15–22 | none | spike, spike-wave |
| 18. twin | 21 | grand mal (12) absence (20) | ? |
| co-twin | 21 | absence (18) grand mal (19) | ? |
| 19. twin | 16–19 | febrile seizure (5) absence (15) Jacksonian (15) | slow burst, spike, spike-wave |
| co-twin | 16–19 | none | spike-wave |
| 20. twin | 8–11 | absence (6) | slow burst, spike |
| co-twin | 8–11 | none | slow burst, spike |

* Died.

among concordant MZ index cases with definite intra-pair difference of symptoms. As expected, the results of this analysis of MZ twins showed evidence of the existence of three etiological categories of chronic epilepsy, as will be indicated in the following sections.

### CONCORDANT MZ TWIN PAIRS WITH REMARKABLE INTRA-PAIR SIMILARITY OF SYMPTOMS (TABLE 3)

Among concordant MZ pairs, eight showed remarkable intra-pair similarity of clinical symptoms. Both twins of seven pairs have or have had grand mal seizures, the frequency of which is slightly dissimilar in one pair and markedly dissimilar among the others (ranging from two times a week to two times a year). In this group index cases and co-twins of three pairs had experienced febrile seizures. Saving the index case and co-twin of one pair (Case 2) in which the onset of grand mal seizures is unknown, all index cases and co-twins with grand mal seizures had the first grand mal convulsion between eight and fourteen years of age.

TABLE 5

*Survey of Clinical Data: Discordant MZ Pairs*

| Case | Age under Observation | Clinical Type of Seizures (Age of Onset) | EEG Dysrhythmia |
|---|---|---|---|
| (Male = Male) | | | |
| 21. twin | 16–20 | Jacksonian (10) psychic (11) | slow burst, spike, spike-wave |
| co-twin | 16–20 | none | none |
| 22. twin | 7–13 | grand mal (4)* | slow burst, spike, spike-wave |
| co-twin | 7–13 | none* | borderline abnormalities |
| 23. twin | 5–11 | grand mal (3) absence (4) | slow burst, spike, spike-wave |
| co-twin | 5–11 | none | borderline abnormalities |
| 24. twin | 2–5 | akinetic (3) | spike, spike-wave |
| co-twin | 2–5 | none | none |
| (Female = Female) | | | |
| 25. twin | 28–32 | grand mal (23) | spike, spike-wave |
| co-twin | 28–32 | none | none |
| 26. twin | 17–22 | grand mal (11) | slow burst, spike, spike-wave |
| co-twin | 17–22 | none | borderline abnormalities |

* Ichthyosis vulgaris with mental deficiency.

In all cases intra-pair difference of the time of onset was less than one year.

All index cases and co-twins of seven pairs with grand mal seizures showed no neurological abnormality. Index cases and co-twins of four male pairs (Cases 1, 2, 4, 5) and one female pair (Case 6) presented mesomorphic body type or a mixed somatotype. Few cases showed severe intellectual deterioration. Thirteen cases were of normal or borderline intelligence, and one case (Case 5) was clearly feeble-minded. Intra-pair similarity of intelligence was marked in six pairs.

Twin index cases and co-twins of three pairs (Cases 1, 2, 4) and an index case (Case 5) showed marked chronic personality disturbance, consisting of reticence, slowness of action, rigidness of attention and sometimes sadistic impulsivity. Two index cases (Cases 1, 2) had been convicted of theft and murder. In these cases the personality pattern was characterized as "viscous temperament."

One twin index case had once attempted suicide, and both twins of this pair (Case 6) had shown a similar personality disturbance in adolescence. The remaining five index cases or co-twins with grand mal seizures showed no reticence or slowness, but appeared to be hypersensitively rigid. The index case and co-twin of one pair (Case 7) had neurotic traits and hysteric convulsions other than epileptic. The index case of another pair (Case 3) also had a history of a suicide attempt. These personality traits might be mild expressions of "viscous temperament."

EEG findings of the cases with grand mal seizures are rather heterogeneous. Out of total of six recorded pairs, five pairs showed obvious paroxysmal dysrhythmia. The remaining two cases were diagnosed as borderline abnormal. A slow burst, the cycle of which is between 4 and 7 per second and always similar among a pair, was concordant in three pairs. A diffuse spiking, indicating intra-pair similarity of detailed patterns in most cases, was concordant in five pairs. Spike-wave complexes, (a 4 cycle per second pattern or variable frequency pattern (21)), were concordant in three pairs

TABLE 6

*Survey of Clinical Data: DZ Pairs*

| Case | Age under Observation | Clinical Type of Seizures (Age of Onset) | EEG Dysrhythmia |
|---|---|---|---|
| | | (Concordant, Male = Male) | |
| 27. twin | 10–18 | focal (9) | slow burst, spike |
| co-twin | 10–18 | febrile seizure (?) | slow burst, spike |
| | | (Concordant, Female = Female) | |
| 28. twin | 12 | absence (10) | spike-wave |
| co-twin | 12 | none | slow burst |
| | | Discordant, Male = Male) | |
| 29. twin | 22–30 | akinetic? (2) absence (16) grand mal (21) | slow burst |
| co-twin | 22–30 | none | none |
| 30. twin | 12–21 | Jacksonian (14) | ? |
| co-twin | 12–21 | none | ? |
| 31. twin | 18 | grand mal (8) | ? |
| co-twin | 18 | none | ? |
| 32. twin | 11 | febrile seizure (1) grand mal (9) | ? |
| co-twin | 11 | none | ? |
| 33. twin | 11 | Jacksonian (4m) psychic (6) | slow burst, spike |
| co-twin | 11 | none | none |
| 34. twin | 5–7 | grand mal (5) | slow burst, spike, spike-wave |
| co-twin | 5–7 | none | borderline abnormalities |
| | | (Discordant, Male = Female) | |
| 35. twin* | 16–23 | grand mal (14) | spike, spike-wave |
| co-twin | 16–23 | none | none |
| | | (Discordant, Female = Female) | |
| 36. twin | 11–14 | grand mal (4) psychic (10) | ? |
| co-twin | 14 | none | ? |
| 37. twin** | 13–14 | Jacksonian (9) | slow burst, spike, spike-wave |
| co-twin | 13 | none | borderline abnormalities |
| 38. twin | 2–11 | myoclonic (3m)*** | spike, spike-wave |
| co-twin | 2–11 | none | none |
| 39. twin | 7–8 | febrile seizure (1) grand mal (4) psychic (7) | slow burst, spike, spike-wave |
| co-twin | 7–8 | none | borderline abnormalities |
| 40. twin | 5–6 | myoclonic (3) grand mal (5)**** | ? |
| co-twin | 5–6 | none | ? |

* Female.
** Died.
*** Epiloia.
**** Phenylketonuria.

TABLE 7
*Concordance of Epilepsy*

| | MZ | | | DZ | | |
|---|---|---|---|---|---|---|
| | Concordant (%) | Discordant (%) | Total | Concordant (%) | Discordant (%) | Total |
| (Diagnosed by Clinical Onset of Seizures) | | | | | | |
| Inouye | 14 (54%) | 12 (46%) | 26 | 1 (7%) | 13 (93%) | 14 |
| Rosanoff *et al.** | 12 (48%) | 13 (52%) | 25 | 9 (8%) | 98 (92%) | 107 |
| Conrad | 20 (67%) | 10 (33%) | 30 | 4 (3%) | 123 (97%) | 127 |
| Lennox *et al.** | 44 (67%) | 22 (33%) | 66 | 11 (12%) | 80 (88%) | 91 |
| (Diagnosed by Clinical Onset of Seizures and EEG Dysrhythmia) | | | | | | |
| Inouye | 20 (77%) | 6 (23%) | 26 | 2 (22%) | 7 (78%) | 9 |

* Corrected (see text).

and discordant in one pair. In both twins of a pair (Case 4), focus of the spike-wave complex was found at frontal lobi. Intra-pair similarity of basic rhythms, which tend to be mildly slow, was seen in frontal or parietal dominance of alpha waves (two pairs), amplitude of alpha waves (four pairs), pattern of alpha waves (four pairs) and mirror image asymmetry of amplitude of alpha and beta waves at occipital leads (one pair).

Both twins of a pair (Case 8) have had only petit mal seizures, with very similar frequencies. The index case is an imbecile, and the co-twin is a moron. No neurological abnormality was found.

While in general there was a striking intra-pair similarity of symptoms, slight intra-pair dissimilarity is also observed in seven pairs with grand mal seizures. In two pairs only one twin of each pair had psychic seizures other than grand mal. Four index cases with slightly more frequent seizures than co-twins had a history of birth disorders or of colitis with disturbance of consciousness. In three pairs (Cases 1, 2, 6) mild slowing of basic EEG rhythms was more obvious in the index cases, which have or have had slightly more frequent seizures than their co-twins.

A twin index case and the co-twin with petit mal and mental deficiency (Case 8) suffered from high fever with somnolence antecedent to the onset of seizures. This history might be interpreted as a coincidental cause of seizures in both twins. It might be safe in this instance to classify the cause as "unknown." No history of antecedent coincidental cerebral disease or trauma is found in any of the other pairs. This fact and the striking intra-pair similarity of the symptoms leads to the conclusion that all cases but a single pair of this group suffer from "hereditary chronic epilepsy," the specific symptoms of which are briefly as follows: grand mal with or without febrile seizures and psychic seizures; onset of grand mal seizures between eight and fourteen years of age; no neurological abnormality; no severe disturbance of intelligence; marked or mild "viscous temperament" and mild slowing of basic EEG rhythms. EEG dysrhythmia, as remarked above, may also be a specific symptom of this category.

### CONCORDANT MZ TWIN PAIRS WITH MARKED INTRA-PAIR DISSIMILARITY OF SYMPTOMS (TABLE 4)

In six MZ pairs both twins suffer or suffered from epileptic seizures, but there are marked intra-pair differences in type, age of onset or frequency. Two index cases (Cases 10, 11) are clearly chronic grand mal epileptics, while their co-twins have a

history of only one grand mal seizure each. Two other index cases (Cases 12, 14) had had febrile seizures in infancy and later manifested typical grand mal or Jacksonian seizures; while their co-twins, showing EEG dysrhythmia, had had only febrile seizures in infancy. The index case of another pair (Case 13) has had frequent Jacksonian seizures, while the co-twin has had only four grand mal seizures. In still another pair (Case 18) the index case has had frequent grand mal convulsions, while the co-twin has had but three, with the onset seven years later than the index case.

Obvious EEG dysrhythmia was found in six other clinically normal MZ co-twins. A total of twelve MZ pairs are concordant with respect to clinical onset of seizures or EEG dysrhythmia, but marked differences of symptoms among one pair are questionable.

Out of twelve index cases, five had a history of birth disorders (asphyxia neonatorum in Cases 12, 13, 16, forceps delivery in Case 17 and coiling of umbilical cord around neck in Case 18), while their co-twins were normally born. The Index case of one pair (Case 14) has a history of head trauma, which did not involve the loss of consciousness, two months prior to the onset of Jacksonian seizures. The index case of another pair (Case 10) has the history of both asphyxia neonatorum and minor head trauma without evidence of loss of consciousness prior to the onset of seizures. Two index cases (Cases 19, 20) present the history of paratyphoid with convulsions and high fever with disturbance of consciousness (presumably measles encephalitis). The index case of one pair (Case 9) had suffered from cerebral arteriosclerosis, confirmed by postmortem pathological examination. The co-twin, who died six years later than the index case, did not have this disease.

The above findings on ten pairs of this group suggest that heredity alone does not cause chronic epilepsy: co-existence of a certain amount of brain damage seems to facilitate or to modify the clinical seizures, or increases the frequency of seizures. The fact that among ten index cases seven were indicated as having signs of brain lesions (Jacksonian convulsions in Cases 13, 16, 19, neurological symptoms in Cases 17, 18 and both signs in Cases 9, 14) tends to confirm the hypothesis. Furthermore, intelligence scores lower than those of co-twins are found in six index cases (mild deterioration in Cases 12, 16, 18, 20 and severe deterioration in Cases 9, 14). EEG records of index cases show slower basic rhythms and more obvious paroxysmal dysrhythmia than the co-twins.

Among ten more mildly affected co-twins no case shows neurological abnormality. Intelligence is within a normal range in all co-twins, excepting one case of a moron (Case 17). A rigid and sensitive personality pattern is seen in all but one co-twin, who showed marked "viscous temperament." EEG dysrhythmia in co-twins is 5 or 6 cycles per second in slow bursts (Cases 14, 16, 20) or diffuse spike (Cases 9, 16, 17, 20).

The symptoms of the more severely affected index cases of these ten pairs are, of course, heterogenous. Four cases have had grand mal seizures, and five cases have had Jacksonian convulsions. Among them four cases had febrile seizures in infancy. The age of onset is reported to be between ten and fourteen years in the case of grand mal seizures, and it varies between two and sixty-four in Jacksonian seizures. Petit mal is seen in four cases, with the onset between six and twenty years of age. As stated above, four cases show neurological symptoms, four cases show slight and two cases show severe deterioration of intelligence. In two severely deteriorated cases personality disturbance is severe. In all other index-cases marked or mild "viscous temperament" was seen. EEG dysrythmia is in slow bursts (1.5–7.5 cycles per second) in seven cases, diffuse spike in six cases, typical or atypical spike-wave complex (2–5 cycles per second) in three cases and

focus of discharge in one case (which is discordant). Borderline abnormalities are seen in one case, and slowing of basic rhythms is found to mild degree in three cases and markedly in one case.

From the findings on the ten pairs of this group the following brief conclusions can be drawn. All but two co-twins of this group suffer or suffered from "mild hereditary epilepsy." Exogenous factors such as birth disorders intensify or modify the symptoms of "mild hereditary epilepsy," and result in "hereditary-exogenous epilepsy" in index cases.

Seemingly contradictory to this conclusion is the absence of obvious intra-pair difference of intelligence in four pairs (Cases 10, 13, 17, 19) and that of EEG dysrhythmia in one pair (Case 20), as well as the fact that some features of EEG dysrhythmia are found more markedly in two mildly affected co-twins (slow burst and diffuse spike in hyperpnea in Case 16 and atypical spike-wave complex in sleep in Case 17). However, these observations may merely show the absence of gross brain lesions in the index cases.

In one pair (Case 15) both twins suffered from presumed vaccination encephalitis at the age of one year. However, possible unreliable information in the history may have failed to disclose relevant exogenous factors. The cause of epilepsy in the index case and in the co-twin must therefore be reported as "unknown."

Both the index case and the co-twin of Case 11 can be classified as "hereditary chronic epilepsy." The history and symptoms of the index case is virtually classic, and that of the co-twin is closely equivalent.

### DISCORDANT MZ TWIN PAIRS (TABLE 5)

Six MZ pairs are discordant with respect to epilepsy. An index case (Case 24) suffered from tuberculous meningitis prior to the onset of akinetic seizures. Another index case (Case 26) suffered from encephalitis japonica at the age of eleven months. The cause of epilepsy in these two index cases is thus exogenous. In three other index cases a history of birth disorders was found (cranial hematoma in Case 21, coiling of umbilical cord around neck in Case 23 and forceps delivery accompanied by questionable cranial hematoma in Case 25). These five index cases are therefore classified as "exogenous epilepsy." Their co-twins are, of course, intact.

The symptoms of "exogenous epilepsy" are also heterogeneous. Grand mal seizures are seen in three cases. One case has had Jacksonian seizures with psychic seizures. Petit mal is seen in two cases. The onset of grand mal seizures in these cases ranges from three to twenty-three years of age. Neurological symptoms are found only in one case (Case 24), though they are expected to be found more frequently. Marked disturbance of intelligence and personality is found in four cases (Cases 21, 23, 24, 26). Distinct intra-pair difference in EEG records is found in all cases. Marked slowing of basic EEG rhythms is seen in all index cases. Slow bursts (2–5 cycles per second) are found in three cases. All show more or less marked diffuse spikes and classical or atypical spike-wave complex (3–4 cycles per second in three cases and 1.5–3 cycles per second in two cases).

The remaining pair (Case 22) is atypical. Both twins have ichthyosis vulgaris and mental deficiency, with only the index case having epileptic seizures. There is no history of an exogenous factor. The epileptic discordance must be understood in terms of an incomplete expression of the gene or genes responsible for ichthyosis vulgaris, which may have pleiotropic effects (12). The index case must therefore be classified as a "specific genetic type" of epilepsy.

### ETIOLOGICAL CATEGORIES OF EPILEPSY

In the foregoing sections all MZ twin index cases and co-twins were classified on the basis of similarity and dissimilarity of symptoms as well as on the basis of past

history into five categories of chronic epilepsy (hereditary chronic, hereditary-exogenous, exogenous, specific genetic and unknown) and two additional categories (mild hereditary and intact). The observed frequency of each category is reported in Table 8. If we try to estimate frequencies among a general population of chronic epileptics, the numbers of cases should be corrected, since MZ co-twins are genetic duplicates of index cases. The numbers of index cases were accordingly counted as one for each pair, both twins of which were classified in the same genetic category. Corrected figures of frequency based on clinical onset of seizures and on clinical onset and EEG dysrhythmia are also shown in Table 8.

TABLE 8

*Frequency of Etiological Categories of Chronic Epilepsy*

| | Uncorrected* | Corrected* | |
|---|---|---|---|
| | | Based upon Clinical Onset | Based upon Clinical Onset & EEG |
| Hereditary Chronic | 16 (44%) | 8 (31%) | 8 (31%) |
| Hereditary-exogenous | 10 (28%) | 5 (19%) | 10 (38%) |
| Exogenous | 5 (14%) | 10 (38%) | 5 (19%) |
| Specific Genetical | 1 (3%) | 1 (4%) | 1 (4%) |
| Unknown | 4 (11%) | 2 (8%) | 2 (8%) |
| Total | 36 | 26 | 26 |
| (Mild Hereditary) | (10) | | |
| (Intact) | (6) | | |
| (Grand Total) | (52) | | |

* See text.

The more or less specific symptoms of first three major categories of chronic epilepsy are summarized in Table 9.

### EXOGENOUS FACTORS CAUSING EPILEPSY

In ten MZ index cases of hereditary-exogenous epilepsy and in five MZ index cases of exogenous epilepsy; various exogenous factors which intensify or modify the symptom

TABLE 9

*Symptoms of Three Categories of Chronic Epilepsy*

| | Hereditary Chronic (16 Cases) | Hereditary-exogenous (10 Cases) | Exogenous (5 Cases) |
|---|---|---|---|
| Type of Seizures | grand mal w/wo febrile & psychic seizures | grand mal/Jacksonian w/wo febrile & psychic seizures<br>petit mal | grand mal<br>Jacksonian<br>petit mal |
| Onset of Seizures | 8–14 (grand mal) | 10–14 (grand mal)<br>6–64 (Jacksonian)<br>6–20 (petit mal) | 3–23 (grand mal)<br>? (Jacksonian)<br>? (petit mal) |
| Neurological Abnormalities | none | often | occasionally (expectedly often) |
| Intelligence Disturbance | not severe | often severe<br>often mild | often severe |
| Personality Disturbance | marked or mild "viscous temperament"* | often mild "viscous temperament"*<br>marked if deteriorated | often marked if deteriorated |
| EEG | | | |
| Slowing of Basic Rhythms | mild | sometimes marked | marked |
| Slow Burst | 4–7 c/s | 1.5–7.5 c/s | 2–5 c/s |
| Diffuse Spike | often | often | marked, very often |
| Spike-wave | often (4 c/s, variable frequency) | often (2–5 c/s) | very often (1.5–4 c/s) |

* See text.

or otherwise contribute to epilepsy, were found. The relative frequencies of these factors are shown in Table 10. The total number given is sixteen, since one index case had the history of both birth disorder and head trauma.

TABLE 10
*Relative Frequencies of Exogenous Factors*

| | |
|---|---|
| Birth Disorders | 9 |
| Infections | 4 |
| Head Trauma | 2 |
| Others | 1 |
| Total | 16* |

* One twin index case had a history of both birth disorder and head trauma.

### FAMILY HISTORY

It is natural to expect that a family history of epilepsy will be found more frequently in hereditary chronic cases and in hereditary-exogenous cases than in exogenous cases. However, in this series there is no excess of history of convulsions in the families of first two categories. Among seven families of hereditary chronic cases and nine families of hereditary-exogenous cases of known history, epilepsy was reported by one family, and transient convulsions in infancy were reported by eight families. Alcoholics with psychotic episodes or with disturbances of consciousness are reported in two families. If combined, ten families (63 per cent) of a total of sixteen families have reported this kind of history. Among four families of exogenous cases, three families have made similar reports. It is interesting that fathers of four hereditary-exogenous cases had a history of convulsive seizures, or alcoholism with loss of consciousness, while no parent of a hereditary chronic case was so reported. Expressivity of the gene or genes responsible for hereditary-exogenous epilepsy may thus be relatively milder than that of the gene or genes responsible for hereditary chronic epilepsy, and seemingly dominant transmission is likely to be found more frequently, though here it is not significant ($p$ (Fisher) = 0.07).

### DISCUSSION

As with the studies by Lennox and Lennox *et al.*, the subjects of the present investigation were not collected by the systematic study method recommended by Luxenburger (13) and succeeding investigators in the field of psychiatric twin study as the best method to obtain an unbiased series of subjects. Most psychiatric twin studies such as those by Conrad (2–4) and Essen-Möller (6) have used only in-patients as subjects. This, of course, is desirable, since investigating all twins among a population of a disease or a syndrome is practically impossible unless a complete registration of health records of a parent population is available. This consideration is most important and may yield biased samples, since rather severe cases are naturally chosen. Kallmann (14) has pointed this out in his study on manic-depressive psychosis. A second serious limitation of the ideal systematic method is the fact that collecting a sufficient number of subjects of a rare disease or syndrome is extremely difficult. Conrad (2–4) had some success on this score in his study of epilepsy, but a relatively small series of subjects, as in the studies of Luxenburger (13), Essen-Möller (6) and Slater (23) does not make it possible to investigate the etiological roles of heredity and environment. Another limitation of the systematic approach is the well-known fact that mortality of twins is higher than that of the general population. From the point of view of careful investigation this makes for serious difficulties. If deceased subjects are involved—as with Conrad's studies—diagnosis of the disease and zygosity is apt to be unreliable.

The present study involved all surviving twins among out-patients and in-patients of a particular diagnostic category, who were personally examined by the author and his collaborators. A possible and unavoidable sampling error has to do with a denial of twinship (or a lack of informa-

tion) by the subjects or their families. This is a basic problem in any investigation of this kind. The fact that only one pair of opposite-sexed DZ twins is involved suggests such an error. Another possible error is an excess of particular cases, selectively reported out of personal interest by doctors other than at the University of Tokyo Neuropsychiatric Clinic. Lennox (18) stated such a possible bias in his study, in which more MZ twins were involved than were expected. In the present study neither an excess of MZ twins nor an excess of concordant pairs was found. There is also no evidence of an excess of female MZ pairs, which was the case in the studies by Lennox (18) and Lennox *et al.* (20). Consequently it is felt that this method of collecting subjects can meet the purpose of this kind of study, if it is carefully carried out.

The excess of same-sexed DZ twins, the observed number of which is 12 with the expected number being 7.94, confirms the findings by Rosanoff *et al.* (21), Conrad (2) and perhaps by Slater (23), though the excess is not significant ($\chi^2$(Yates) = 1.13, $p > 0.20$). Recently Stern (24) has offered theoretical evidence of overrepresentation of DZ ascertained for the presence of a genetic trait. Epilepsy can, however, not be a genetic trait. Conrad (2) concluded there is a genetic relation between epilepsy and DZ twin birth, but the conclusion can not be confirmed. Family history of epilepsy, infantile convulsions or alcoholism with psychotic episodes or with disturbance of consciousness is found in the histories of 67 per cent of MZ twin pairs and 56 per cent of DZ twin pairs, excepting cases of a specific genetic type. On the other hand, birth disorders appear to be excessive in DZ twins, since they are more likely accompanied by DZ twin births (33 per cent among forty-six MZ twin births and 45 per cent among twenty-two DZ twin births, in both of which the presence or absence of birth disorder is known). However the difference among the two zygosities is again not significant ($\chi^2 = 1.1$ $p > 0.30$); the definite cause of this excess in same-sexed DZ twins is still obscure.

The concordant ratio of MZ twins, based upon the clinical onset of seizures, is lower than that of Conrad (2). It seems that this result may be partly due to the collection of subjects among mildly affected out-patients. In spite of this the important role of heredity was in strong agreement with earlier studies.

As expected, etiological categories can well be classified on the bases of concordance and past history of each MZ case. This result is in agreement with the conclusion of the study on the family of epileptics by Harvald (7) and with the rather general belief that epilepsy is not a disease entity. The extended application of the twin study method would therefore be an useful approach to the complex etiologies of this syndrome.

One striking finding is the relative mildness of symptoms seen in hereditary chronic epilepsy. This observation may eventually displace the concept of idiopathic epilepsy. Differential diagnosis of this type has thus to be based upon the lack of severe symptoms. Among mild symptoms, 4 cycle per second spike-wave complex and spike-wave complex of variable frequency pattern may be of diagnostic value. The term "symptomatic epilepsy" was not employed, since both exogeneous agents and specific gene or genes such as responsible to ichthyosis vulgaris and epiloia can produce epileptic seizures as a symptom. Among heterogeneous symptoms of hereditary-exogenous epilepsy and exogenous epilepsy, signs of brain damage such as neurological symptoms, intelligence and personality deterioration, and slowing of basic EEG rhythms are noteworthy. The signs are, in general, more distinct in pure exogenous epilepsy. Other symptoms are also variable in two categories, but the range of variability in age

of onset and in the cycle of EEG dysrhythmia is not always wider in exogenous epilepsy than in hereditary-exogenous epilepsy.

The estimated frequency of hereditary chronic epilepsy was approximately thirty per cent, and that of pure exogenous epilepsy approximately twenty per cent (of all chronic epileptics). Similar estimates can be made from the data of Conrad (3, 4) and Lennox *et al.* (20), both of whom classified cases into concordance and discordance on the basis of the clinical onset of seizures. Conrad (4) classified MZ cases into idiopathic and symptomatic epilepsy. According to this classification the number of cases in his study is twenty-two (73 per cent) in idiopathic, and eight (27 per cent) in symptomatic epilepsy. The corrected figures become 68 and 32 per cent respectively. However his classification cannot entirely be confirmed from the present view of the etiology of epilepsy. Conrad reported many cases which might well be classified as specific genetic type or of cause unknown, in idiopathic epilepsy, and also seemed to overemphasize the disposition of idiopathic epilepsy. Five of his pairs concordant with respect to particular symptoms (tendency to hydrocephalus, microcephaly, pigmentation on extremities and truncus, mental deficiency with malformations and fibroma) may be classified as of the specific genetic type. Four concordant MZ pairs with marked intra-pair difference of symptoms (the more mildly involved twin in one pair suffered presumable meningitis, the more mildly involved twin in another pair was born by forceps, a pair without known difference of history and a pair the co-twin of which died early) should be classified as of cause unknown. The frequency of idiopathic epilepsy is then diminished and becomes 38 per cent. There is no case classified as hereditary-exogenous epilepsy in Conrad's subjects. Exogenous epilepsy becomes thus 27 per cent, specific genetical type 19 per cent and of unknown cause 15 per cent. The absence of hereditary-exogenous epilepsy in Conrad's subjects may be due to incomplete personal histories, since his study is statistical in nature and the series included deceased cases and cases lacking complete information. Lennox *et al.* (20) reported that among MZ twins thirty-five pairs (53 per cent) were both chronic, nine pairs (14 per cent) were one chronic and one transient, and twenty-two pairs (33 per cent) were one chronic and one free of seizures. These investigators did not report a great deal of case detail, and their figures do not correspond exactly to the first three major categories of chronic epilepsy used in the present study. The low frequency of hereditary chronic epilepsy in the present study and of idiopathic epilepsy in Conrad's study is undoubtedly due to the criterion of strict similarity of symptoms in concordant MZ twins. The frequency of exogenous epilepsy in the present study is slightly higher than those of earlier reports.

The relative importance of birth trauma here reported is in agreement with the conclusion drawn by Rosanoff *et al.* (21). According to Conrad's data on his discordant MZ pairs, the history of head trauma (three cases), febrile disease with convulsion and hemiplegia (one case) and uremia (one case) seem to have been responsible as exogenous factors. To establish the accurate frequencies of exogenous agents, a larger number of cases would of course be required.

The expectation of finding significant numbers of epileptics or patients with seemingly related diseases among families of hereditary chronic cases and hereditary-exogenous cases has not been fulfilled. This may in part be due to the lack of EEG records for relatives of patients, and partly to the generally good genetic prognosis of epilepsy, as reported by Conrad (5) and Harvald (7). To differentiate hereditary chronic epilepsy on the basis of family history is thus often difficult. Alström's (1) particular conclusion, which approaches a

denial of the role of heredity in epilepsy, may have been a result of the difficulty of differentiating each etiological category on the basis of family history.

The gene or genes responsible for hereditary chronic epilepsy need not be of complete penetrance or complete expressivity. However, there was no MZ pair in which one twin suffered from typical hereditary chronic epilepsy and the co-twin was intact or only mildly affected. This fact suggests the probable high penetrance of the gene or genes responsible for the disorder, but investigating such discordant pairs is important to substantiate this conclusion.

In Case 11 the index case presented almost typical symptoms of hereditary chronic epilepsy, and the co-twin suffered from psychic seizures equivalent to grand mal convulsions. In other words the marked intra-pair difference in the course of the disease might be explained by the concept of variability of expressivity of the gene or genes responsible for hereditary chronic epilepsy. This may also explain the intra-pair difference as to type of first seizure in Case 10, whereas the difference in severity of symptoms may be on the basis of exogenous factors having affected the index case.

With respect to the expression of genes responsible for hereditary-exogenous epilepsy and mild hereditary epilepsy, a seemingly dominant transmission was suggested. However nothing is known as to whether the genes are different from those of hereditary chronic epilepsy, and whether the genes responsible for each clinical type of mild hereditary epilepsy (subclinical seizures, febrile seizures and several grand mals) are identical or not. Such a conclusion could only be drawn from detailed and extensive study of complete family histories.

## SUMMARY

Twenty-six monozygotic and fourteen dizygotic twin index cases (including two cases born as triplets) which suffered from chronic epilepsy, were collected among out-patients and in-patients at various clinics in Japan. The numbers of twin pairs and triplet sets, as well as the numbers of zygosities of twins, do not significantly differ from expected numbers in the general population of twins and triplets. All index cases and their co-twins were personally examined, and most monozygotic twins were repeatedy re-examined. A brief survey of clinical symptoms was presented.

Fifty-four per cent of monozygotic twins and seven per cent of dizygotic twins were concordant with respect to the clinical onset of seizures. A relatively low concordant ratio of monozygotic twins was probably due to the inclusion of mildly affected out-patients. With respect to the clinical onset of seizures or EEG dysrhythmia, seventy-seven per cent of monozygotic twins and twenty-two per cent of dizygotic twins were concordant. The roles of genetic and environmental factors, as well as the essential non-unity of epilepsy as a disease were confirmed.

Of eight concordant monozygotic pairs, showing remarkable intra-pair similarity of symptoms, seven index cases and their co-twins had a uniform symptom complex and no antecedent history of coincidental brain damage. They were classified as "hereditary chronic epilepsy." The specific symptoms of this category consist of grand mal with or without febrile seizures and psychic seizures, onset of grand mal between eight and fourteen years of age, no neurological abnormality, no severe intelligence disturbance and mild slowing of basic EEG rhythms. A typical personality pattern involved slowness of action, rigidity of attention and a tendency to sadistic impulsivity. Slow bursts (4–7 cycles per second), diffuse spike and spike-wave complexes of 4 cycles per second and with variable frequency pattern, may also be specific. One index case and the co-twin of a remarkably similar pair were classified as of cause "unknown."

Of twelve concordant monozygotic pairs with marked intra-pair dissimilarity of

symptoms, ten index cases were found having antecedent history of birth disorders, head trauma, infections with convulsions or with disturbance of consciousness, or cerebral arteriosclerosis. They were classified as "hereditary-exogenous epilepsy," while their co-twins, having suffered from subclinical seizures, febrile seizures or several grand mal convulsions, were classified as "mild hereditary epilepsy." A monozygotic index case and co-twin without known difference of antecedent history were classified as of cause unknown. The index case and the co-twin of a remaining pair were classified as hereditary chronic epilepsy, and the intra-pair difference in the course of the disease was explained by the concept of variability of specificity of the gene or genes responsible for hereditary chronic epilepsy. The symptoms of hereditary-exogenous epilepsy were seen to be heterogeneous: they included grand mal or Jacksonian seizures with or without febrile seizures, psychic seizures, petit mal, a wide range of age of onset, signs of mild or severe brain damage, intelligence and personality disturbance and occasionally marked slowing of basic EEG rhythms. The symptoms of mild hereditary epilepsy were subclinical seizures, febrile seizures or several grand mal seizures, rigid and sensitive personality traits and relatively mild EEG dysrhythmia.

Five index cases out of six discordant monozygotic pairs were found to have prior histories of birth disorders or infectious diseases of the brain. They were classified as "exogenous epilepsy," while their co-twins were intact. The symptoms of exogenous epilepsy were also found to be heterogeneous. One index case and the co-twin had ichthyosis vulgaris and mental deficiency; the index case was classified as "specific genetical type" of chronic epilepsy. The discordance with respect to convulsions among the pair was explained on the basis of an incomplete expression of the gene or genes responsible for ichthyosis vulgaris.

Frequency of each etiological category among chronic epileptics was estimated. The estimated frequency of hereditary chronic epilepsy was approximately thirty per cent, and that of exogenous epilepsy was approximately twenty per cent. The results were compared with those of earlier studies. Relative mildness of symptoms of hereditary chronic epilepsy was stressed as a basis for differential diagnosis of this category.

Relative frequencies of exogenous agents which intensify or modify symptoms in concordant monozygotic index cases with marked intra-pair dissimilarity of symptoms or in discordant monozygotic index cases, were estimated. Among various factors birth disorders were found to be of relative importance.

No excessive family history of epilepsy, infantile convulsions, or alcoholism with psychotic episodes or with disturbance of consciousness, was found in hereditary chronic epilepsy and hereditary-exogenous epilepsy. Difficulties in differentiating each category on the basis of family history were pointed out. Dominant transmission was suggested in hereditary-exogenous epilepsy or in mild hereditary epilepsy.

A statistical excess of same-sexed dizygotic twins, in agreement with the findings of earlier investigators, was assumed to be due to birth disorders as a frequent accompaniment of dizygotic twin births. Problems of methodology, subject selection and the sampling method of the present study were discussed. The extended application of the twin study method was suggested as a useful technique in the approach to the complex etiologies of these syndromes.

## REFERENCES

1. Alström, C. H. A study of epilepsy in its clinical, social and genetic aspects. Acta psychiat. et neurol., supp. 63, pp. 1–284, 1950.
2. Conrad, K. Erbanlage und Epilepsie. Untersuchungen an einer Serie von 253 Zwillingspaaren. Ztschr. ges. Neurol. u. Psychiat., **153**: 271–326, 1935.
3. Conrad, K. Erbanlage und Epilepsie. II. Ein Beitrag zur Zwillingskasuistik. Ztschr. ges. Neurol. u. Psychiat., **155**: 254–297, 1936.
4. Conrad, K. Erbanlage und Epilepsie. III. Ein

Beitrag zur Zwillingskasuistik. Ztschr. ges. Neurol. u. Psychiat., **155**: 509–542, 1936.

5. Conrad, K. Erbanlage und Epilepsie. IV. Ergebnisse einer Nachkommenschatsuntersuchung an Epileptikern. Ztschr. ges. Neurol. u. Psychiat., **159**: 521–581, 1937.
6. Essen-Möller, E. Psychiatrische Untersuchungen an einer Serie von Zwillingen. Acta psychiat. et neurol., supp. 23, pp. 1–200, 1941.
7. Harvald, B. *Heredity in Epilepsy*. E. Munksgaard, Copenhagen, 1954.
8. Inouye, E. Investigation on the problems involved in zygosity diagnosis of twins. Studies on twins, pp. 1–20, Nihon Gakujutsu Shinkokai, Tokyo, 1954 (Japanese).
9. Inouye, E. Zygosity diagnosis of Japanese twins by means of Essen-Möller's formula. Studies on twins. II, pp. 9–13, Nihon Gakujutsu Shinkokai, Tokyo, 1956 (Japanese).
10. Inouye, E. A review on zygosity diagnosis of twins. Jap. J. Human Genet., **1**: 24–31, 1956 (Japanese w. English résumé).
11. Inouye, E. Frequency of multiple birth in three cities of Japan. Am. J. Human Genet., **4**: 317–320, 1957.
12. Inouye, E., Haruhara, C. and Murobuse, K. Ichthyosis vulgaris and neuropsychiatric symptoms. Psychiat. et neurol. jap., **60**: 909–916, 1958 (Japanese w. English abstract).
13. Luxenburger, H. Psychiatrisch-neurologische Zwillingspathologie. Zentralbl. Neur. u. Psychiatr., 56: 145–180, 1930.
14. Kallmann, F. J. *Heredity in Health and Mental Disorder*, pp. 128–129. Norton, New York, 1953.
15. Kamide, H. and Fukuda, T. A study on epileptic twins. Studies on twins, I, pp. 142–168, Nihon Gakujutsu Shinkokai, Tokyo, 1954 (Japanese).
16. Kamide, H. and Fukuda, T. A study on epileptic twins, II. Studies on twins, II, pp. 302–318, Nihon Gakujutsu Shinkokai, Tokyo, 1956. (Japanese).
17. Kamide, H. Observation on forty-two twin pairs with epilepsy. Psychiat. et neurol. jap., **59**: 1259–1302, 1957 (Japanese w. English abstract).
18. Lennox, W. G. Sixty-six twin pairs affected by seizures. A. Res. Nerv. & Ment. Dis., Proc., **26**: 11–33, 1946.
19. Lennox, W. G. The heredity of epilepsy as told by relatives and twins. J. A. M. A., **146**: 529–536, 1951.
20. Lennox, W. G. and Jolly, D. H. Seizures, brain waves and intelligence tests of epileptic twins. A. Res. Nerv. & Ment. Dis., Proc., **33**: 325–345, 1954.
21. Rosanoff, A. J., Handy, L. M. and Rosanoff, I. A. Etiology of epilepsy, with special reference to its occurrence in twins. Arch. Neurol. & Psychiat., **31**: 1165–1193, 1934.
22. Silverman, D. Clinical correlates on the spike-wave complex. Electroencephalog. & clin. Neurophysiol., **6**: 663–669, 1954.
23. Slater, E. *Psychotic and neurotic illness in twins*. Privy Council Medical Report Series 278, Her Majesty's Stationery Office, London, 1953.
24. Stern, C. The ratio of monozygotic to dizygotic affected twins and frequencies of affected twins in unselected data. Acta genet. et med, gemellol., **7**: 313–320, 1958.

# THE APPEARANCE OF A SKATOLE DERIVATIVE IN THE URINE OF SCHIZOPHRENICS

AKIRA NAKAO, PH.D.[1] AND MARJORIE BALL, B.S.

Interest in the possible presence of abnormal aromatic and indolic metabolites in the urine of schizophrenics has been stimulated in the past few years by the work of Young *et al.* (12) and McGeer *et al.* (7–9). Using similar paper chromatographic techniques as these investigators, we have studied the urine chromatographic pictures of a group of male, chronic schizophrenic patients and have detected one Ehrlich positive, indolic compound which appears significantly more often in the urine of schizophrenics than in that of control subjects. This compound, termed Compound X, appears to be identical with the 6-sulfatoxyskatol described by Horning, Dalgliesh and co-workers (1–3) and reported to appear in the urine of patients afflicted with malabsorption syndrome, certain anemias, and in Heinz Body formations.

## MATERIALS AND METHODS

The subjects used in this experiment were part of a cooperative study carried out by the central office of the Veterans Administration on the chemotherapeutic effect of tranquilizers. The medication being given the patients was not known during the course of the study. Morning urine samples were obtained once a week over a six week period, concentrated *in vacuo*, and an amount of urine corresponding to 100 micrograms of creatinine was chromatographed overnight on paper in a solvent system consisting of butanol - acetic acid - water (4:1:5) or isopropanol-ammonia-water (80:2:18). The papers were sprayed with Ehrlich's reagent (2 per cent dimethylaminobenzaldehyde in 2N HCl) and dried in a current of air in a hood. The Compound X color complex developed fairly rapidly and tended to fade with time and was, therefore, graded as to intensity as soon as color developed. The intensity of the spots obtained were graded by eye with rating values of from 0 to 3. The blue Ehrlich spot of Compound X gave an $R_f$ of .58 in butanol-acetic acid-water and $R_f$ of .73 in isopropanol-ammonia-water.

Controls for the study were male aides who lived on the hospital grounds and whose meals were the same as those of the patients.

## RESULTS AND DISCUSSION

Table 1 shows that of 23 experimental subjects 18 were adjudged positive for Compound X on the basis of spot ratings of 0.5 or greater. The 0.5 value taken as the dividing point is arbitrary. A value less than 0.5 would mean that the spot was detected under the conditions of the chromatography in less than one-half of the assays. The intensity of spots obtained from week to week was relatively constant. The data, furthermore, show that there is no correlation between the appearance of Compound X and the drug treatment. However, it may be worthy of note that the negative findings in the experimental group were all diagnosed as paranoid schizophrenics. In the control group (Table 2) three positive findings from 14 subjects were obtained and all three of these subjects were older men. The significance of these latter observations cannot be assessed without more data.

Only a partial purification of Compound X by means of repeated paper chromatography and elution has been effected. Properties of the compound indicative of its acidic nature were its retention by an anion ex-

[1] Research Laboratory, Veterans Administration Hospital, Palo Alto, California.

TABLE 1

*Occurrence of Compound X in the Urine of Male Chronic Schizophrenics*

| Patient No. | Age | No. of Assays | Positive Results | Total* Points | Average† Points | Medication | Diagnosis |
|---|---|---|---|---|---|---|---|
| 1 | 37 | 4 | 4 | 6 | 1.5 | Chlorprom. | Catatonic |
| 2 | 46 | 4 | 4 | 4 | 1.0 | Placebo | Mixed |
| 3 | 42 | 4 | 4 | 7 | 1.8 | Placebo | Mixed |
| 4 | 36 | 4 | 4 | 4 | 1.0 | Phenobarb. | Paranoid |
| 5 | 31 | 5 | 5 | 6 | 1.2 | Phenobarb. | Catatonic |
| 6 | 49 | 4 | 4 | 8 | 2.0 | Promazine | Hebephrenic (Mixed) |
| 7 | 37 | 4 | 4 | 11 | 2.8 | Placebo | Catatonic |
| 8 | 41 | 4 | 2 | 2 | 0.5 | Phenobarb. | Hebephrenic |
| 9 | 40 | 5 | 5 | 7 | 1.4 | Phenobarb. | Catatonic |
| 10 | 27 | 4 | 4 | 5 | 1.3 | Promazine | Catatonic |
| 11 | 40 | 4 | 4 | 6 | 1.5 | Promazine | Catatonic |
| 12 | 41 | 4 | 4 | 5 | 1.3 | Promazine | Paranoid |
| 13 | 41 | 5 | 5 | 12 | 2.4 | Promazine | Hebephrenic |
| 14 | 44 | 5 | 0 | 0 | 0.0 | Placebo | Paranoid |
| 15 | 43 | 5 | 4 | 9 | 1.8 | Chlorprom. | Paranoid |
| 16 | 34 | 4 | 4 | 6 | 1.5 | Promazine | Paran. Catatonic |
| 17 | 35 | 5 | 0 | 0 | 0.0 | Phenobarb. | Paranoid |
| 18 | 30 | 5 | 0 | 0 | 0.0 | Promazine | Paranoid |
| 19 | 39 | 5 | 2 | 2 | 0.4 | Promazine | Paranoid |
| 20 | 39 | 4 | 3 | 3 | 0.8 | Chlorprom. | Paranoid |
| 21 | 47 | 5 | 4 | 6 | 1.2 | Phenobarb. | Paranoid |
| 22 | 35 | 4 | 4 | 4 | 1.0 | Chlorprom. | Paranoid |
| 23 | 33 | 4 | 0 | 0 | 0.0 | Phenobarb. | Undiff. or Paranoid |

* Based on spot intensity values rated from 0 to 3.

† Total points/Number of assays.

TABLE 2

*Occurrence of Compound X in the Urine of Controls*

| Subject No. | Age | No. of Assays | Positive Results | Total* Points | Average† Points |
|---|---|---|---|---|---|
| 1 | 60 | 4 | 3 | 3 | 0.8 |
| 2 | 29 | 5 | 0 | 0 | 0.0 |
| 3 | 48 | 4 | 0 | 0 | 0.0 |
| 4 | 36 | 5 | 1 | 1 | 0.2 |
| 5 | 24 | 3 | 0 | 0 | 0.0 |
| 6 | 28 | 4 | 0 | 0 | 0.0 |
| 7 | 47 | 3 | 0 | 0 | 0.0 |
| 8 | 36 | 4 | 0 | 0 | 0.0 |
| 9 | 22 | 5 | 0 | 0 | 0.0 |
| 10 | 25 | 4 | 0 | 0 | 0.0 |
| 11 | 57 | 4 | 1 | 2 | 0.5 |
| 12 | 65 | 5 | 5 | 8 | 1.6 |
| 13 | 22 | 4 | 0 | 0 | 0.0 |
| 14 | 33 | 4 | 1 | 1 | 0.3 |

* Based on spot intensity values rated from 0 to 3.

† Total points/Number of assays.

change resin (Dowex 1-Cl) and not by cation exchange resin (Dowex 50-H) and its similar migration to that of indoxylsulfate on paper electrophoresis. The compound, in crude urine, was stable to 0.1 N NaOH at 100° C for 1 hour but was completely destroyed in 0.1 N HCl under these conditions. The skatolic nature of the compound was suggested by Dr. C. E. Dalgliesh (personal communication), and on administration of skatole to rats (either feeding via stomach tube or by intraperitoneal injection) a compound was obtained in urine with the identical chromatographic properties as Compound X. Both this compound and Compound X isolated from the patients yielded inorganic sulfate after digestion in 6N HCl at 100° for 1 hour. From these results and reference to work of Dalgliesh and co-workers (1–3) we believe Compound X to be 6-sulfatoxyskatole. Compound X was also produced in approximately the same quantities in rats that were pretreated for 2 days with antibiotics (6 mg tetracycline, 15 mg Kanamycin twice daily) before the administration of skatole. Indican concentration in the urine was markedly lowered by this treatment. Quite likely, therefore, the bacteria in the gut converts indolic products to skatol, the skatol is absorbed and converted into Compound X via hydroxylation and esterification with sulfate by the tissues of the rat. That the bacterial flora was involved in the production of Compound X in the patients was shown by the oral administration of tetracycline (250 mg, four times daily) over a five day period to two patients showing the greatest amount of Compound X in their urine. Compound X was abolished (chromatographic detection) on the first day after administration of antibiotic in patient #1 and by the second day in patient #2. Indican, which is also produced by the intestinal flora, decreased daily during the administration of antibiotic but was still detected in substantial amounts even after 5 days of treatment.

Compound X is quite likely identical with the Compound Q described by Leyton (6)

and provisionally identified by him as skatoxyl sulfate. It may also be the same as Compound *a* as reported by Riegelhaupt (10) which was reported to be present in 12 of 14 schizophrenics and in two of seven non-schizophrenic controls. However, Compound *a* was reported to be unstable in 0.1 N NaOH in which Compound X was found to be stable.

The need for considering nutritional state, chronic infections, and characteristic intestinal flora of institutionalized patients in analyzing urine excretion picture in schizophrenics has been pointed out by Kety (5) and Horwitt (4). Compound X, which is tentatively identified as 6-sulfatoxyskatole, would seem to be the resultant of one of these complicating factors. The abolishment of this compound from urine by the administration of antibiotic would seem to place it in the same category as indican, which also has been reported to be increased in the urine of the schizophrenics (11). The conditions that favor the production of sulfatoxyskatole in institutionalized, chronic schizophrenic patients are unknown but their actions may be mediated by something as simple as constipation, a characteristic institutional bacterial flora, or by more subtle biochemical changes brought about by the schizophrenic state. The significance, if any, of sulfatoxyskatole in schizophrenia remains to be determined. That hydroxyskatoles, the precursors of sulfatoxyskatole (1–3) are damaging to red blood cells and to hemoglobin, and their role in certain anemias, Heinz Body formations and malabsorption syndrome have been reported.

## SUMMARY

A compound identified as 6-sulfatoxyskatole has been found to occur more often in the urine of chronic schizophrenics than in normal controls. Bacterial action in the gut is probably responsible for its presence, however, since the oral administration of antibiotics results in the elimination of this compound from urine.

## REFERENCES

1. Dalgliesh, C. E., Kelly, W. and Horning, E. C. Excretion of a sulphatoxy derivative of skatole in pathological states of man. Biochem. J., 70: 13p, 1958.
2. Horning, E. C. and Dalgliesh, C. E. The association of skatole-forming bacteria in the small intestines with the malabsorption syndrome and certain anemias. Biochem. J., 70: 13p, 1958.
3. Horning, E. C., Sweeley, C. C., Dalgliesh, C. E. and Kelly, W. Mammalian hydroxylation in the 6-position of the indole ring. Biochim. et biophys. acta, 32: 566–567, 1959.
4. Horwitt, M. K. Fact and artifact in the biology of schizophrenia. Science, 124: 429–430, (1956).
5. Kety, S. S. Biochemical theories of schizophrenia. Science, 129: 1528–1532, 1959.
6. Leyton, G. B. Indolic compounds in the urine of schizophrenics. British M. J., 2: 1136–1139, 1958.
7. McGeer, E. G., Brown, W. T. and McGeer, P. L. Aromatic metabolism in schizophrenia. II. Bidimensional urinary chromatography. J. Nerv. & Ment. Dis., 125: 11–15, 1957.
8. McGeer, P. L., McGeer, E. G., and Gibson, W. C. Aromatic excretory pattern of schizophrenics. Science, 123: 1029–1030, 1956.
9. McGeer, P. L., McNair, F. E., McGeer, E. G. and Gibson, W. C. Aromatic metabolism in schizophrenia I. Statistical evidence for aromaturia. J. Nerv. & Ment. Dis., 125: 1–10, 1957.
10. Riegelhaupt, L. M. Investigations of the urinary excretion pattern in psychotic patients. J. Nerv. & Ment. Dis., 127: 228–231, 1958.
11. Sano, I., Über die kalte Millon-Reaction beim schizophrenen Formenkreis und den Trager derselben. Folia psychiat. et neurol. japonica, 8: 219–231, 1954.
12. Young, M. K., Jr., Berry, H. K., Beerstecher, E., Jr. and Berry, J. S. Metabolism patterns of schizophrenic and control groups. Biochemical Institute Studies, Publication No. 5109, pp. 189–197. Univ. of Texas Austin, Texas, 1951.

# EFFECTS OF SERUM FROM SCHIZOPHRENICS ON EPINEPHRINE-SENSITIVE ELEMENTS IN THE RABBIT BRAIN[1]

BRUNO MINZ, M.D.[2] AND EDWARD J. WALASZEK, PH.D.[3]

The discovery of similarities between experimental and natural psychoses has led to the elaboration of chemical theories as speculative explanations of the origin and nature of mental disorders. Some of these theories implicated epinephrine and possible metabolites of epinephrine (2).

Recent developments have shown that the role of the adrenal medullary hormone is not strictly confined to its classical effects on blood pressure and carbohydrate metabolism, but that it has the property of acting directly upon neuronal aggregates in the central nervous system. For example, it has been demonstrated (7) that small doses of epinephrine, injected intravenously or intra-arterially into cats or rabbits, prolong the duration of electrically induced seizures and shorten the period of extinction subsequent to electrical stimulation. Also extensor and flexor reflexes can be modified by a direct effect of epinephrine on the brain stem reticular formation (8). Other experiments carried out by Minz, Remond and McCulloch (9) on the monkey have indicated that local application of epinephrine on the motor arm area of the cerebral cortex causes an increase in duration and intensity of the period of over-stimulation subsequent to a stimulus eliciting movement.

The presence of norepinephrine and epinephrine has been detected in the hypothalamic area (15). This area is considered a projection zone of the sympathetic system, and the catecholamine content of this tissue has been found susceptible of undergoing characteristic modifications under the action of reserpine (3) and of iproniazid (14), two compounds which strikingly affect psychic reactions.

Clinical observations have shown that the epinephrine level of blood decreases during normal sleep and increases during awakeness (13). The injection of that hormone can produce anxiety, self-concern and aggravate conflict sustained symptoms. Its effect presents itself, according to Lindemann (4) "as a variety of changes in psycho-pathological behavior which have a definite dynamic structure, namely withdrawal from the outside and reinforcement of inner experiences."

Combined physiological and clinical data thus suggest the working hypothesis that the reactivity of central structures may be a major factor in normal cerebral function and possibly in cerebral disorders. In this preliminary report we wish to present the effects of serum from schizophrenic patients on the cardiovascular responses elicited by the topical application (1, 10) of epinephrine to the exposed cerebral cortex of rabbits.

## METHODS

The experiments were carried out on male adult albino rabbits anesthetized with urethane (1.0–1.5 gm./kg.). The cerebral hemispheres were exposed and the dura opened. Mean systemic arterial blood pressure was measured via a cannula in the left femoral artery; the right vena saphena was cannulated for intravenous injections. A very small piece of filter paper (3 to 5 mm. sq.) moistened with a freshly prepared 5 per cent solution of epinephrine bitartrate

[1] This investigation was supported by a Senior Research Fellowship SF-72 from the Public Health Service and by a grant, M-1902, from the Public Health Service.

[2] Present address: Laboratoire de Pathologie et Therapeutique Generale, Universite de Paris, France.

[3] Department of Pharmacology, University of Kansas Medical Center, Kansas City, Kansas, and Osawatomie State Hospital, Osawatomie, Kansas.

in Ringer's solution (pH 6.0) was placed on the left frontoparietal zone of the cerebral cortex. After a very short contact (30 seconds) the systemic blood pressure rises (20–50 mm.Hg) maintains a maximum for 0.5 to 2 min. and then decreases to its initial value.

A thorough pharmacodynamic analysis has indicated that this cortically induced pressor effect possesses the characteristics of an entirely central phenomenon and is due to the liberation of a hypertensive agent from the anterior hypothalamus (6). Repeated application of epinephrine to the same cortical area found to be the most sensitive to the adrenal hormone, produces a progressively increasing response.

The serum was generally used the same day on which it was withdrawn from the patients. In our preliminary experiments the volumes used for each administration were from 1 to 5 ml. The number of injections ranged from one to nine with intervals of two to four days. The tests were performed from three hours to nine days after the last treatment.

We have determined that the most favorable conditions for these experiments were as follows: Rabbits receive 5 ml. of patient's serum (freshly withdrawn and used the same day) intravenously and 16–18 hours later epinephrine was applied topically to the exposed cerebral cortex. Another experimental design which we used was as follows: Rabbits received 2 ml. of patient's serum subcutaneously twice at four-day intervals. The epinephrine was applied topically within 24 hours after the last injection of serum. A total of sixty-eight rabbits was used in these experiments. Twenty rabbits received the serum intravenously. The remainder received the two subcutaneous injections.

The experimental sera were obtained from 30 different female patients, all of whom had been hospitalized for a least five years. They were carefully screened; epileptics, mentally deficient or lobotomized patients, as well as patients with physical handicaps (blindness, deafness) or gross associated medical syndromes were excluded. Age ranged from 25 to 50 years. The diagnosis of "schizophrenia" was established after a very careful psychiatric examination and observation and through a battery of psychological tests. All forms of that disease were represented (simple, undifferentiated, catatonic, paranoid and hebephrenic). The patients had received no medication for a period of at least four weeks prior to the withdrawal of the serum and were closely supervised by specially trained aides in a separate research ward.

The normal serum with which the control rabbits were premedicated was derived from thirty-five different employees of the Osawatomie State Hospital. The experimental and control subjects received the same diet and the latter like the former, lived within the institution. Sera from normal volunteers were obtained, administered and tested under the same conditions as those withdrawn from the patients. A total of forty-eight rabbits was used in these experiments.

Seven rabbits received serum from seven healthy pregnant women (5th to 9th months of pregnancy). Six animals were injected with serum from six patients suffering from conditions involving stress such as arthritis, asthma, diabetes, liver damage, ulcerative collitis and pernicious anemia[4]. All these sera were administered in two subcutaneous injections of two ml. each at intervals of four days and the tests were performed one day after the last injection.

## RESULTS

Forty-one animals injected with serum from normal individuals were found to respond to cortically applied epinephrine with usual blood pressure rises. The manometric differences obtained after one single application varied between 6 and 61 mm. Hg

[4] These patients were selected by Dr. A. Klotz, Dept. of Medicine, Kansas University Medical Center.

with a mean value of 30.5; those recorded after repeated topical administrations reached 20 to 74 mm./Hg, with a mean value of 22 mm./Hg. These figures show a fair accordance with those found by Chamorro and Minz (1) in normal non-treated rabbits. Seven animals gave diminished hypertensive responses to the cortical epinephrine. The cardiovascular responses to cortical applications of epinephrine observed in animals after pretreatment with normal human serum presented the phenomenon of increased sensitization (1). Such sera thus failed to produce any characteristic modification of the usual blood pressure effects engendered by topical application of epinephrine to the cerebral cortex. Typical results obtained with an animal which had been submitted to a treatment with serum from a mentally normal volunteer, are illustrated in Figure 1.

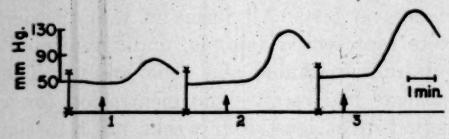


FIG. 1. Rabbit blood pressure: Animal premedicated with serum from a normal volunteer. At 1, 2 and 3, cardio-vascular responses to successive local application of epinephrine bitartrate (5%) to the same fronto-parietal area of the exposed cerebral cortex at 10 minute intervals.

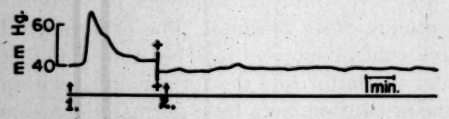


FIG. 2. Rabbit blood pressure: Animal pretreated with serum from a schizophrenic patient. At 1, an intravenous injection of epinephrine (10 mcgm.). At 2, a cortical epinephrine application (5th application). This illustrates the inhibition of the usual hypertensive reaction to cortically applied epinephrine.

FIG. 3. Rabbit blood pressure: Animal premedicated with serum from a schizophrenic patient. At the arrows 1 and 3, cortically applied epinephrine. At 2 and 4, intravenous injections of epinephrine (5 mcgm.). This record illustrates the reversal of the usual hypertensive response to the cortical application of epinephrine.

Fifty rabbits pretreated with serum from schizophrenic patients did not respond with the usual blood pressure rises to the cortical application of epinephrine. Twenty-one animals did not present any reaction even after repeated topical administration of the adrenal hormone on the same fronto-parietal area. Five to 12 successive applications made at regular intervals of 10 to 15 minutes were found to be ineffective, whereas intravenous injection of epinephrine solutions (10 mcgm.) produced the usual hypertensive responses (Figure 2). Eighteen rabbits showed slight depressor reactions (14 to 20 mm. Hg and less), appearing in some instances immediately after the application of epinephrine on the area, in others after delays of three to 12 minutes (Figure 3). In some cases one cortical application of epinephrine caused the appearance of a series of alternating small pressor and depressor effects (Figure 4).

Inhibitions as well as reversals of cardio-

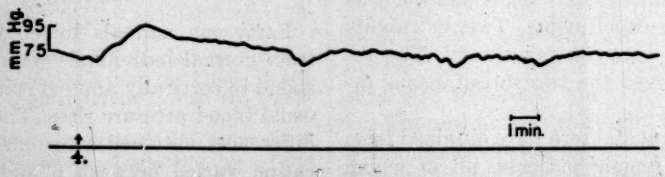


FIG. 4. Rabbit blood pressure: Animal premedicated with serum from a schizophrenic patient. The topical application of epinephrine (4th application) on the fronto-parietal area (at the arrow) engenders a very small rise in blood pressure, but this effect is prolonged and followed by a series of hypotensive reactions.

vascular reactions to cortically applied epinephrine occurred under similar experimental conditions; they have been observed in animals pretreated with a series of subcutaneous injections on the one hand, and in others, tested 16–18 hours after one intravenous administration. Both responses probably representing different degrees of an inhibitory process, were recorded without any special distinction in rabbits receiving serum from patients who exhibited catatonic, hebephrenic, paranoid or mixed schizophrenic reactions. Eighteen rabbits pretreated with serum from schizophrenic patients reacted with usual pressor responses to cortical application of epinephrine and eleven gave a diminished hypertensive response. Table 1 summarizes all the results.

Six rabbits injected with serum from pregnant women responded with pressor effects to cortically applied epinephrine; the manometric differences varied from 14 to 52 mm.Hg after one single topical administration (mean value: 23) after repeated applications on the same cortical area values between 20 and 70 mm.Hg when obtained (mean value: 42.3). In one case, the manometric difference was not higher than 10 mm. Hg and did not increase after successive topical applications of epinephrine. Six rabbits pretreated with serum from six different patients with various organic diseases reacted to cortically applied epinephrine with the usual hypertensive effects.

TABLE 1

*Cardiovascular Responses to Cortically Applied Epinephrine*

| Pretreatment of Rabbits | No. of animals | Usual hypertensive response | Diminished hypertensive response | Abolition of hypertensive response | Reversal of hypertensive response (depressor effect) |
|---|---|---|---|---|---|
| Serum from normal volunteers | 48 | 41 | 7 | 0 | 0 |
| Serum from schizophrenic patients | 68 | 18 | 11 | 21 | 18 |
| Serum from pregnant women | 7 | 6 | 1 | 0 | 0 |
| Serum from patients with other disease conditions | 6 | 6 | 0 | 0 | 0 |

## DISCUSSION

The results have shown that the hypertensive response to cortically applied epinephrine was typically elicited in rabbits pretreated with serum from normal human volunteers, but that it usually undergoes characteristic modification in rabbits pretreated with serum from schizophrenic patients. Administered to sixty-eight animals, the patient serum abolished that reaction in twenty-one and reversed it in eighteen. Eleven rabbits showed very small and irregular hypertensive responses. The remaining eighteen rabbits did not differ from those injected with normal serum. In fact, thirteen of them gave the normal reaction, while five showed an exaggerated normal response.

In a double blind experiment (a series of nine animals) we were able to correctly assign the animals receiving schizophrenic serum 66 per cent of the time. This compares favorably with our studies where we found abnormal responses in about 60 per cent of the patients tested. In another double blind experiment using serum from patients in another institution, we were able to make the correct diagnosis only 40 per cent of the time. We thus regard these experiments as tools for the study of the physiology and biochemistry of schizophrenia and not as a biological test for this disorder.

The number of aberrant results appears relatively small considering the following facts: 1) Schizophrenia often presents phases with alternating spontaneous aggravation and remissions. Serum from these patients may consequently contain varying concentrations of abnormal metabolites according to the phase at which that serum has been withdrawn. 2) Different recipient

animals may show different degrees of affinity or resistance to effects of patient's serum. Thus, serum from the same catatonic patient has been found to produce inhibition in two rabbits and enhancement of cortically induced pressor effects in another animal. The exaggerated responses obtained in some experiments may have been due to the appearance of an initial sensitization possibly followed later on by an inhibition but it could also constitute a phenomenon in itself. Clinical observations supporting the pharmacodynamic results reported in this article have been made by Reiter (12) who obtained very striking but short lasting remission in severe schizophrenics after quasi-total transfusions with blood from mentally normal individuals.

The cardiovascular response to cortically applied epinephrine which has been typically modified in animals pretreated with serum from schizophrenics implies the activity of hypothalamic elements. That same reaction was considerably augmented by reserpine (5), a tranquilizer, which can lower the content of norepinephrine in the brain stem (3). Experiments performed in our laboratory have shown that animals pretreated with serum from schizophrenics presented significantly higher epinephrine and norepinephrine levels in the hypothalamus than control animals pretreated with serum from normal volunteers (16, 17). Thus the cortically applied epinephrine pressor response showed a general correlation with changes in the catecholamine concentrations of hypothalamic centers. According to recent findings of Spector and co-workers (14) the administration of iproniazid, a monoamine oxidase inhibitor, to rabbits increases the norepinephrine content in the brain stem. Our results indicated that iproniazid administered under identical experimental conditions was capable of inhibiting the cardiovascular response to cortically applied epinephrine (11). It would thus be very tempting to assume that the inhibition or reversal of the cortical response detected in animals pretreated with schizophrenic serum may be due to an accumulation of catecholamines in the hypothalamus.

These experiments led us to conclude that schizophrenic serum may contain a substance or substances which alter the reactivity of cerebral structures to topically applied epinephrine.

## SUMMARY

It has been shown that serum from schizophrenic patients can abolish or reverse the usual hypertensive reactions which can be obtained with a topical application of epinephrine to the exposed cerebral cortex of rabbits.

Serum from normal volunteers, pregnant women, and patients with various organic diseases did not alter the response of topically applied epinephrine.

Evidence for the inhibition of the usual hypertensive response in animals pretreated with schizophrenic serum was discussed from the standpoint of catecholamine content of the rabbit hypothalamus.

A conclusion was reached that serum from schizophrenic patients may contain a substance or substances which altered the reactivity of cerebral structures to topically applied epinephrine.

## REFERENCES

1. Chamorro, A. and Minz, B. Sensibilization a distance par l'adrenaline appliquee sur le cortex cerebral du lapin. C. R. Soc. Biol., **150**: 299–303, 1956.
2. Hoffer, A., Osmond, H. and Smythies, J. Schizophrenia: a new approach. J. Mental Sci., **100**: 29–45, 1954.
3. Holzbauer, M. and Vogt, M. Depression by reserpine of the noradrenaline concentration in the hypothalamus of the cat. J. Neurochem., **1**: 8–11, 1956.
4. Lindemann, E. The psychopathological effect of drugs affecting the vegetative system. Am. J. Psychiat., **91**: 983–1008, 1934.
5. Minz, B. Actions de drogues tranquillisantes sur la reaction du cortex cerebral a l'adrenaline. C. R. Soc. Biol., **151**: 432–436, 1957.
6. Minz, B. and Chamorro, A. Sur une action cortico-hypothalamique declenchee par l'adrenaline. C. R. Acad. Sci., **240**: 454–455, 1955.

7. MINZ, B. AND DOMINO, E. Effects of epinephrine and norepinephrine on electrically induced seizures. J. Pharmacol. Exper. Therap., **107:** 204–218, 1952.
8. MINZ, B. AND KING, E. Epinephrine modification of the effects of brain stem stimulation of the patellar and linguomandibular reflexes. J. Pharmacol. Exper. Therap., **106:** 407, 1952.
9. MINZ, B., REMOND, A. AND MCCULLOCH, W. S. Local effects of epinephrine on the cerebral cortex. Proc. Soc. Expt. Biol. Med., **83:** 306–308, 1953.
10. MINZ, B. AND WALASZEK, E. J. Sur la presence de substances biologiquement actives dans le serum de schizophrenes. C. R. Acad. Sci., **244:** 1974–1976, 1957.
11. MINZ, B. AND WALASZEK, E. J. Sur le mecanisme de l'inhibition de la reaction corticale a l' adrenaline chez des lapins traites avec du serum de schizophrenes. C. R. Acad. Sci., **246:** 1326–1328, 1958.
12. REITER, P. J. Untersuchungen zur beleuchtung der intoxikations theorie bie der dementia praecox mit besonderer berucksichtigung der versuche mit totaltransfusionen. Ztschr. f. d. ges. Neurol. u. psychiat., **160:** 598–614, 1938.
13. RENTON, G. H. AND WEIL-MALHERBE, H. Adrenaline and noradrenaline in human plasma during natural sleep. J. Physiol., **131:** 170–175, 1956.
14. SPECTOR, S., PROCKOP, P., SHORE, A. AND BRODIE, B. Effect of iproniazid on brain levels of norepinephrine and serotonin. Science, **127:** 704, 1958.
15. VOGT, M. The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. J. Physiol., **123:** 451–481, 1953.
16. WALASZEK, E. J., SMITH, C. M. AND MINZ, B. Effect of serum from schizophrenic patients on neurohumors in rabbit brain. Federation Proc., **17:** 416, 1958.
17. WALASZEK, E. J. Brain neurohormones and cortical epinephrine pressor responses as affected by schizophrenic serum. Int. Rev. Neurobiol., **2:** 1960 (in press).

BRIEF COMMUNICATION

# PSYCHOLOGICAL FACTORS IN THE DUMPING SYNDROME

PAUL ZUKIN, M.D.[1] AND IRA WEINER, PH.D

Clinical impression suggests that emotional instability predisposes to the postgastrectomy "dumping" syndrome, but the literature does not contain any satisfactory data on this point (1). In this context this paper briefly reports observations of the relation of emotional disturbance to the development of postgastrectomy symptoms. Various authors report that from three to thirty-three per cent of individuals who undergo subtotal gastric resection as treatment for duodenal ulcer manifest this postoperative syndrome with symptoms including nausea and occasional vomiting, epigastric fullness, sweating, palpatation and weakness. In the majority of those who experience these complaints, the onset occurs within two weeks after surgery. Usually the severity of the syndrome decreases with time. However, at least one-third of these individuals continue to show disability from their symptoms a year or more after surgery.

## PROCEDURE

Personality studies were conducted on a series of male veterans with chronic duodenal ulcers at the Wadsworth Veterans Administration Hospital in Los Angeles by one of us (I.W.) as partial fulfillment of the requirement for a doctorate in clinical psychology. A Group Short Form of the Minnesota Multiphasic Personality Inventory (MMPI) was used in this evaluation. This inventory has the most extensive clinical validation of any objective personality test and has been found valuable diagnostically and prognostically in a wide variety of clinical problems. (2). Not only is this instrument objective and comprehensive, but in addition it possesses unique validity measures which indicate, to a degree, test-taking attitudes, malingering, and whether the respondents understood the various items.

Within two weeks from the time of the personality evaluation, eleven of the patients underwent a Billroth II type of subtotal gastric resection without vagotomy. Indication for surgery was intractibility, hemorrhage, or pyloric obstruction, either singly or in combination.

Without prior knowledge of the results of the pre-operative personality studies, the other author (P.Z.) interviewed the patients, twelve to twenty-four months after surgery, and the operative result was rated on the basis of the following criteria:

Excellent: unrestricted as to activity and diet, free of symptoms except perhaps for occasional minimal dumping.

Good: No complaints other than frequent mild, or occasionally moderate, manifestation of dumping and necessitating care in regard to certain items of diet.

Poor: Severe dumping, persistent gastric distress, inability to gain weight, failure to obtain relief by medical and dietary measures.

## RESULTS AND DISCUSSION

The data are summarized in Table 1. All three of the severely neurotic and one of the two moderately neurotic ulcer patients in this series had poor results of gastric resection, while those with minimal or mild emo-

[1] Veterans Administration Center, Los Angeles, California; School of Medicine, University of California at Los Angeles.

TABLE 1

*Relation of Emotional Disturbance and Result of Subtotal Gastrectomy in Duodenal Ulcer*

| Patient No. | Age | Duration of ulcer in years | Indications for surgery* | Degree of emotional disturbance | Predicted result of surgery† | Postoperative evaluation |
|---|---|---|---|---|---|---|
| 1. | 61 | 12 | I & O | Severe | Unfavorable | Poor |
| 2. | 42 | 8 | I | Severe | Unfavorable | Poor |
| 3. | 60 | 10 | I & H | Severe | Unfavorable | Poor |
| 4. | 66 | 20 | I | Moderate | Unfavorable | Excellent |
| 5. | 34 | 4 | I & H | Moderate | Unfavorable | Poor |
| 6. | 58 | 13 | I & H | Mild | Favorable | Excellent |
| 7. | 47 | 8 | I & H | Mild | Favorable | Excellent |
| 8. | 37 | 8 | L & H | Minimal | Favorable | Good |
| 9. | 56 | 10 | I & H | Minimal | Favorable | Good |
| 10. | 62 | 14 | I & P | Minimal | Favorable | Good |
| 11. | 60 | 10 | H | Minimal | Favorable | Good |

* I = intractability; O = obstruction; H = hemorrhage; P = perforation.

† MMPI profile indicating moderate or severe neuroticism was basis for predicting unfavorable results of operation.

tional disturbance—on the basis of MMPI data—had either good or excellent results. We do not know whether this means that elective gastric surgery should not be done at all in the severely disturbed individuals or whether they might better tolerate a lesser procedure such as vagotomy with drainage. Certainly it seems reasonable to suggest that a personality evaluation should be an integral factor in the decision for elective surgery in patients with duodenal ulcer. A replication of this investigation is indicated.

## SUMMARY

An attempt to relate pre-operative personality characteristics to the subsequent development of dumping manifestations in eleven patients who underwent subtotal gastrectomy for chronic duodenal ulcer, indicates that the individual with mild or moderate emotional disturbance may have a satisfactory operative result, while a severely disturbed individual is apt to have a poor result.

In this group, using the Minnesota Multiphasic Personality Inventory as an indicator of neuroticism before operation, it was possible to predict with considerable accuracy those patients who later developed the dumping syndrome.

## REFERENCES

1. Harvey, D. H., St. John, F. B. and Volk, H. Peptic ulcer: Follow up results after partial gastrectomy-analysis of failures. Ann. Surg., 138: 680–688, 1953.
2. Hathaway, S. R. and McKinley, J. C. *The Minnesota Personality Inventory*. Rev. ed. Univ. of Minnesota Press, Minneapolis, 1943.
3. Ivy, A. C., Grossman, M. I. and Bachrach, W. H. *Peptic Ulcer*. Blakiston, Philadelphia, 1950.

BRIEF COMMUNICATION

# PAPER CHROMATOGRAPHIC STUDY OF URINES OF NORMAL AND SCHIZOPHRENIC INDIVIDUALS

CLARA H. WILLIAMS, PH.D.,[1] EDNA C. GORDON, B.A. AND FREDERICK W. BARNES, JR., M.D., PH.D.

The possibility of detecting abnormal metabolic changes in schizophrenia has led to investigations of many different substances; in general the reports on their relationship to the disease are conflicting. McGeer *et al.* (1) reported that schizophrenic individuals excrete larger quantities of "aromatic" substances than do normal individuals, and their conclusions were based upon the number and intensity of color of diazo-coupling spots appearing on unidimensional paper chromatograms. The writers undertook a similar study and found no significant differences between the urinary patterns of 131 schizophrenic patients from three different categories and normal subjects (Table 1).

In the present study, bi-dimensional chromatography was used as a more sensitive method for detecting possible differences in occurrence and concentration of urinary components in schizophrenic patients. The methods described below represent those selected from an extensive survey of the effect of different papers, solvent systems and stains on the chromatographic pattern.

## MATERIALS AND METHODS

Urines were collected from: 1) twenty newly admitted, disturbed, male schizophrenic patients under 50 years old; 2) seventeen male hospital employees under 50; 3) seventeen males, 50 years or older, with a diagnosis of general paresis, and 4) thirteen patients from group (1) and nine male hospital employees who were on the same hospital diet.

The first voided morning urine from individual patients was collected and, within an hour, stored at −20°C. After the urine was thawed, and pH and specific gravity determined, a 100 ml. aliquot was centrifuged, the precipitate was discarded, and the supernatant was evaporated at 40°C to a volume of 10 ml. on a water bath, at atmospheric pressure. After being cooled and recentrifuged, the supernatant was evaporated further to a final volume of 5 ml. Two ml. of this were mixed with 200 ml. of methanol, and the mixture was poured into a glass column (13 mm. in diam.) containing 18 cm of MgO and SiO (Florisil), to which were then added two successive 30 ml. portions of methanol containing 1 per cent water. The filtrate from the 260 cc., representing the alcohol-soluble substances in the urine, was evaporated to a volume of 2 ml. on a water bath, as Fraction A. Sixty ml. of water in two 30 ml. aliquots was added to the Florisil column, and this filtrate (water-soluble substances) was collected and concentrated, as Fraction B.

Twenty-five microliters of each fraction (representing 0.4 ml. of the original urine) were applied to Whatman #1 filter paper sheets (18.5″ x 22.5″) for bi-dimensional descending chromatography, using the solvent systems propanol, ammonium hydroxide (15N) and water in the ratio of 4 vols:1 vol:1 vol in the first dimension across the filter paper, and butanol, glacial acetic acid and water in the ratio of 4 vols:1 vol:1 vol in the second dimension. To develop the spots the papers were air-dried for 24 hours.

[1] Psychophysiologic Research Laboratory, Veterans Administration Hospital, Perry Point, Maryland.

TABLE 1

*Chromatographic Ratings of Urines of Various Samples*

| Type of Male Patient | N | Chromatographic Ratings (Number & Intensity of Spots) |
|---|---|---|
| Chronic schizophrenic (under 50 yrs, no drugs) | 58 | 15.2 ± 2.7 |
| Chronic schizophrenic (over 50, long hospitalized) | 15 | 8.9 ± 1.6 |
| Acutely disturbed schizophrenics (under 50, newly hospitalized) | 25 | 16.3 ± 1.9 |
| Control (normals) | 33 | 15.2 ± 1.4 |

The fluorescent spots were noted under each of two ultra-violet light sources (2537Å and 3600Å) and papers were then sprayed with a mixture of equal volumes of a 9 per cent (weight) solution of diazotized sulfanilic acid and a 10 per cent (weight) solution of sodium carbonate.

## RESULTS

The methanol-soluble fractions of the urines yielded a total of 42 definite substances which either stained with diazotized sulfanilic acid or were fluorescent. The water soluble fraction yielded a total of 29 substances. Not all of these components appeared in every urine and, except for one substance, their frequency of occurrence did not differ greatly among the urines of the various patients and the normals. When the total number of spots on the chomatograms from the urines of each population group was divided by the number of each group (Table 2), no significant trends were evident. It is clear from this evidence that there is no marked increase in the excretion of "aromatic" substances in the schizophrenic populations tested. When size and intensity of color of the spots were estimated by eye, no differences were noted.

TABLE 2

*Diazo-Positive Spots in Urinary Chromatograms of Various Populations**

| | Number of Chromatograms | Fraction A Average Number of Spots per Chromatogram | Fraction B Average Number of Spots per Chromatogram |
|---|---|---|---|
| Schizophrenics | 20 | 10.7 | 11.9 |
| Normals | 17 | 15.7 | 12.8 |
| Paretics | 17 | 11.9 | 13.1 |
| Schizophrenics† | 13 | 12.9 | 15.1 |
| Normals† | 9 | 13.4 | 15.9 |

* Further particulars regarding the Rf values and frequency of occurrence of spots available from authors upon request.

† On the same diet.

In Fraction A, a substance with Rf values of 0.28 vs. 0.18, giving a red color with the diazo reagent, was found in more of the schizophrenic and the paretic than in the normal individuals, except when the latter were on the same diet as the patients. Further work with this substance is planned with other subjects.

## SUMMARY

A survey of metabolites in individual urines of various population groups indicated a definite regularity in the qualitative occurrence of these substances, regardless of diet, degree of illness, drug ingestion, etc. The chromatographic map consisted of 42 alcohol-soluble substances and 29 water-soluble substances. Only one area showed any suggestion of relationship to schizophrenia.

## REFERENCE

1. McGeer, P. L., McGeer, E. G., and Gibson, W. C. Aromatic excretory pattern of schizophrenics. Science, **123**, 1029–1030, 1956.

STENGEL, E. AND COOK, NANCY G. *Attempted Suicide: Its Social Significance and Effects.* Chapman and Hall, London, 1958. 136 pp. 25s

This monograph is a welcome addition to the literature on attempted suicide and is worth the careful study of psychiatrists and of investigators in the field of suicide. The authors have personally examined 453 cases of attempted suicide from three different hospitals—210 at follow-up and 243 on admission. There is an emphasis on the complex of motivation of attempted suicide, *e.g.*, the authors point out that death is probably not the only goal of attempted suicide and that other goals and motives must be considered. There is also due emphasis on the necessity for studying a number of different attempted suicide populations before drawing firm conclusions concerning the total entity, attempted suicide.

Despite the detailed presentation of the results obtained from the examination of such a large number of cases, some of the difficulties inherent in the methods of study and in the way in which the data are presented are sufficiently serious to throw into question the interpretations which the authors give to their findings. One of these difficulties is that the investigators did not have the opportunity to personally examine and follow-up the same patients. In each instance, patients followed up were not examined on admission, and patients examined on admission were not followed up. Some of the other problems will be discussed below.

The emphasis in this study has been on the social significance and effects of the suicide attempt. These social implications have been subsumed under four headings: the immediate social setting at the time of the attempt, the effects of the attempt on the patient's life situation and on his relationship to the environment, the ordeal character of the attempt, and the appeal character of the attempt.

The authors describe the social setting of the patient at the time of the suicide attempts and, where possible, contrast it with a group of successful suicides. They conclude that the suicide attempts are socially oriented. The findings concerning the social setting of the attempts, when compared with a group of successful suicides, were that the attempted suicides were alone in a house or flat in one-third of the cases, whereas the successful suicides were alone in two-thirds of the cases. There was little difference, however, between the groups with regard to whether some one was actually present in the room or not. In the various attempted suicide groups, in three to 12 per cent of the cases there was someone in the room, and in the successful suicide group there was someone in the room in three per cent of the cases. In only about one-third of the attempts did the patient initiate his own rescue and only in another one-tenth of the cases was the rescuer expected. In less than one-half the attempts, therefore, was the "rescue" planned. It appears, therefore, that the majority of settings for the suicidal attempts could as well be interpreted as not being primarily socially oriented. Other studies of attempted suicide have suggested that the clinical diagnosis of the patient is strongly related to, for example, whether or not the patient is alone at the time of the attempt. This point is not discussed in the monograph.

The effects of the attempt on the patient's life situation and on his relationship to his environment are discussed under ten headings which include, among others, hospitalization; invalidism; removal from scene of conflict; changes in human relationships—improved personal relationship, rupture of a personal relationship, and greater dependence; arousal of community; changes in the

state of isolation in which the patient had been living prior to the attempt; and effect on a repetitive pattern of suicidal attempts. The fact of hospitalization is given as a social effect of the suicide attempt by the authors. Although hospital admission undeniably is an effect of the attempt, its meaning and importance are dimmed by the fact that all patients had to have been hospitalized in order to get into the study. Other than the fact of hospitalization, effects of the attempt described in the two groups followed-up included changes in existing human relationships—for better or for worse—occurring in 33 per cent of one group and 43 per cent of the second group; changes in the patient's mode of life in eight per cent of each group; no recurrence of suicide attempts during the follow-up period despite other attempts prior to the index attempt in 27 and 83 per cent, respectively; and a change in the previous state of isolation, excluding hospitalization, in 33 per cent in one group. The significance and interpretation of these figures seem to be equivocal because of three factors: 1) the absence of explicit criteria for deciding whether a change was due to the suicide attempt, to the patient's illness, or to the ordinary trials and pleasures of life; 2) the failure to relate changes observed to diagnosis or age; 3) the absence of control group(s) for helping to decide whether a change was due to the attempt.

There are no data given to indicate that the suicide attempt is considered by the patients to be an ordeal, except for one anecdote about a schizophrenic patient.

The appeal character of the suicide attempt is one of the major points made by the authors. They state, "We regard the *appeal character* of the suicidal attempt, which is usually unconscious, as one of its essential features, but it is certainly not the only one that determines its purpose" (p. 22). The appeal is elsewhere (p. 117) described as, " . . . an appeal to the human environment for help, irrespective of whether or not the person is aware of it . . . The present writers maintain that this appeal function is inherent in most, if not all, suicidal attempts although the person committing the act is as a rule unaware of this. This conclusion can be drawn both from the behavior pattern and its effects on the environment." The difficulties with the concept of appeal character are four-fold. First, no way is presented to decide whether or not an individual suicide attempt served as an appeal. Second, the fact that society responded to the suicide attempt by offering help is not conclusive evidence that the purpose, conscious or unconscious, of the attempt was to call forth such help. Yet the authors seem to assume that the reception of help is *prima facie* evidence that the purpose of the suicide attempt was an appeal for help. Third, only a hospitalized group was studied, which by definition has called forth at least medical help from society. The help forthcoming might be nil or much less in suicide attempts that do not reach the hospital. Fourth, the statement that appeal can be present without awareness on the part of the patient and the fact that no criteria are given for ruling out the presence of appeal makes it possible for an investigator to observe appeal in each and every patient or, alternatively, to fail to observe it in any patient. The present study cannot, therefore, demonstrate the appeal aspect of suicide attempts to be either valid or invalid.

This brings up a final point. The authors state, "The impossibility of comparing data collected by various authors restricts the value of their work and hampers progress in research" (p. 34). This is a well-taken point; however, the present study, in many of its aspects, does little to remedy this situation. The reason for not being able to compare the present work with any future studies of even these same problems is that the authors do not give explicit criteria for diagnosis, for deciding whether the effects observed in follow-up are due to the

attempt, for deciding whether the attempt has an ordeal character, and for deciding whether the attempt has an appeal character. This is particularly disturbing in this study, because it does contain new ideas, is a careful work on a large number of patients, and is concerned with a serious problem.

Eli Robins

CROXTON, FREDERICK C. *Elementary Statistics with Applications in Medicine and the Biological Sciences.* Dover Publications, Inc., New York, 1959. vii + 376 pp., illus. $1.95

This volume is a paperback edition, unabridged and corrected, of a work first published in 1953 under a slightly different title. Assuming no previous study of statistics and only a very modest knowledge of mathematics, the author treats a series of topics ranging from tabular and graphic presentation, through descriptive statistics to elementary statistical inference. As the title indicates, the book is intended primarily as an introductory text for students in the medical and allied fields.

There are a number of features which enhance the pedagogic and reference value of the book. Practically all illustrative material is based on actual, not hypothetical, data. Charts and tables are copious, clearly presented, and well annotated. A vocabulary of statistical symbols precedes each chapter. Tables in the appendix are accompanied by figures showing graphically what is covered by each, *e.g.* one-tail versus two-tail probabilities.

Professor Croxton is the co-author of two earlier texts, one of which was used in the reviewer's first course in statistics. Fifteen years later, he often refers to this well-worn volume—in preference to more recently published works—to clarify a basic point. Instructors and students both should welcome this inexpensive introduction to statistical methods and techniques. Generalizing from a small, non-random sample, they may still be making good use of it fifteen years hence.

A. B. Silverstein

BRACELAND, FRANCIS J., ED. *The Effect of Pharmacologic Agents on the Nervous System.* The Williams and Wilkins Co., Baltimore, 1959. xi + 488 pp., illus. $13.50

This book consists of the proceedings of the 1957 meeting of the Association for Research in Nervous and Mental Disease. Braceland, in his preface, writes that the conference was supposed to "delineate, at least in general lines, the status of neuro- and psychopharmacology, the directions in which these were moving and, if possible, new directions which would be rewarding to clinicians and researchers alike."

There are twenty-six papers in all. Two of these, by Braceland and Merritt, are short introductory statements that served as keynote addresses for the conference and one, by Rioch, summarizes the conference. The rest report research and review literature in widely varied areas, such as the neurochemistry of anticonvulsant drugs (Woodbury and Esplin), structural and molecular facets of cerebral responses to drugs (Grenell, May, McElroy and Mendelson), the effects of CNS depressants on spinal cord reflexes (Abdulian, Martin and Unna), the pharmacologic treatment of movement disorders (Corbin), fact and fantasy in the use of sedatives and hypnotics (Lasagna), the use of placebos (Wolf), opiate antagonism and drug abuse (Wikler), metabolic defects affecting the CNS (Jervis), stimulants (Himwich), pharmacologic studies of the phenothiazines (the Killams), structural effects of tranquilizers (Roizin, True and Knight), hormonal effects on brain function (Hoagland and Freeman), and the use of biologicals in CNS diseases (Turner).

Readers whose primary interest is in behavior should read Brady's well integrated account of the operant conditioning approach to drug evaluation. A vastly differ-

ent approach to the problem is outlined by Lehmann in a paper on drug evaluation in humans. This author has chosen to concentrate on very simple tasks that he thinks measure "basic mental functions" or "fundamental psychological processes." The battery he originally used will serve to indicate what Lehmann is trying to do. It consisted of critical flicker-fusion frequency, the illumination threshold for the disappearance of a negative after-image, tapping speed and simple reaction time. Lehmann believes that "we can make such isolated sectors of behavior meaningful if we view them against the background of our dynamic theories of man, and it would seem to be justified to view such simple functions as integral parts of the total field of ego organization" (p. 137). The reviewer wonders how viable will be the offspring of this strange union of psychophysiology and dynamic psychology.

The use of tranquilizers is discussed by two authors. Kline reviews the literature on reserpine and the newer phenothiazines (and also devotes space to the "energizer" iproniazid), and Bennett reviews the literature on the phenothiazines alone. The value of both these reviews is lessened greatly by the failure of the authors to weight differentially studies that are models of scientific procedure and studies that make no attempt whatsoever to control bias.

One caveat: the papers by Heath, Leach and Cohen on the production of psychotic behavior by abnormal substances in the serum and by Abood on chemical concepts of mental health and disease should be read in conjunction with Kety's recent critical account of the area (Science, **129**: 1528–1532; Science, **129**: 1590–1596, 1959).

Victor G. Laties

LAMM, STANLEY S. *Pediatric Neurology.* Lansberger Medical Books, Inc., New York, 1959. xii + 495 pp., illus. $12.90

Current interest in diseases of the nervous system of infancy and childhood is more widespread than it has ever been in the past, so that a new text in pediatric neurology finds a receptive audience. Unfortunately, the book itself is disappointing and not likely to satisfy either the neurologist or the pediatrician. The book is succinctly written but it is this reviewer's opinion that the clinical and neuropathological discussions are not comprehensive enough for a text devoted to such a specialized discipline of medicine. On the other hand, it is evident that the author has had considerable experience with certain important pediatric problems such as "cerebral palsy" and discussions concerning management of these are adequate. Up-to-date references follow discussions of each disease or group of diseases. The photographs are poorly reproduced, although one unhappily gets the impression that many of the illustrations would otherwise be of considerable interest. The book is not well edited.

Philip R. Dodge

HALL, EDWARD T. *The Silent Language.* Doubleday and Co., New York, 1958. 240 pp. $3.95

This book represents an interesting attempt, by an anthropologist, to present some of the subtle non-verbal aspects of culture that often cause communication difficulties between peoples of different ethnic groups. After giving examples of some of the problems that arise in cross-cultural technological and social innovation, the author attempts to systematize his analysis of culture. In doing this he uses a model of scientific linguistics and employs such analogues as "isolates," "sets," and "patterns." In the opinion of this reviewer this attempt to formalize and systematize "culture" by breaking it down into about one hundred analytical sub-categories is less than successful. The classification often appears to be forced and does not appreciably add depth or clarity to existing modes of analysis.

The most rewarding part of this volume is concerned with the presentation and dis-

cussion of communication difficulties stemming from the subtle meaning of gestures and tacit value positions that are assumed to be universal. The importance of understanding these forms of non-verbal aspects of communication is crucial for the work of any innovator in a foreign society. Perhaps the most important function of such as understanding is given by the author himself: "The ultimate reason for such a study is to learn more about how one's own system works." To be exposed to the contrast of a "tradition-oriented" culture makes one keenly aware of his own assumptions concerning the attitudes toward pragmatic experimentation and the inevitability of progress. The concept of time as a flow of events rather than a quantity that can be broken up into discrete units certainly makes a Westerner more conscious of his own behavior as well as that of some non-Western groups.

In regard to the stated purpose, the book should have a more than casual interest for those engaged in psychotherapy. The recent volumes by Hollingshead and Redlich, and Myers and Roberts point to the fact that the cultural gap between social classes in this country has contributed to the considerable difficulties of the psychiatrist in treating individuals of a lower socioeconomic status. The often heard label "not suitable for psychotherapy" may represent a lack of understanding and a confession of inability to adapt treatment methods to sub-cultural differences. The barrier of the "silent language" is, perhaps, analogous to that faced by the innovator working on the societal level. The present volume should be thought-provoking in this connection.

Seymour Parker

WEWETZER, K. H. *Das hirngeschädigte Kind.* Georg Thieme Verlag, Stuttgart, 1959. viii + 117 pp. $4.70

This monograph is concerned with etiology, psychopathology and differential diagnosis of congenital brain damage. Experimental analysis of factors involved and the comparison with carefully selected control groups are utilized to give prognostic criteria for brain-damaged children. Specific recommendations are given in an excellent summary. It is stated that congenital brain damage leads to difficulties in areas of intellectual functioning and affective behavior, since basic functions must have undergone changes. However, these basic disturbances are viewed as factors of process. "A brain damaged child does not perform a task less capably than a healthy one, but it does so in a different manner." Therefore, the focus of diagnosis and therapy must be dynamically oriented from the very beginning. The treatise is highly recommended as a well documented and basic contribution to education and guidance of the handicapped child.

KOLLE, K. *Psychiatrische und Nervenklinik.* Georg Thieme Verlag, Stuttgart, 1959. xvi + 252 pp. $4.70

Dr. Kolle is one of the more thoughtful psychiatric writers of our time. He holds the chair of Psychiatry and Neurology at the University of Munich and thus, by rank and recognition may regard himself a lineal descendant of Kraepelin. There remains small doubt that his psychiatric convictions rest on the foundations of the great clinician and classifier. His book *Psychiatrische und Nervenklinik* contains 17 lectures in psychiatry and neurology as the core of his undergraduate teaching. Though many of the 187 case presentations seem at times foreign in idiom even more than in language, this academic anthology is of interest as it raises questions of style and content in teaching.

The selection of patients conveys the impression that the author believes in an ultimate explanation or even solution of psychiatric illness on the basis of biological and physiological research. He also does not subscribe to a view which sees a possible continuum between neurosis and psychosis.

On the other hand, the lectures are grouped around human problems, rather than conventional psychiatric disease entities, and the thematic content of each demonstration admits to intra- and interpersonal conflict as the disruptive force. Yet, disturbances of non-psychotic proportions seem relegated to constitution and circumstance. Could this be in contradiction to an expressively stated humanistic and holistic approach in trying to comprehend mental as well as emotional disease?

In his preface, the author says that his conversation with the patient should be considered one of the focal points in demonstration. His previous acquaintance with each patient and perhaps also limitations of time during an individual lecture tend to create the impression of a rather directive type of interviewing. Though pertinent observations are perhaps more readily highlighted this way, the omission of associative material on the patient's part may render the psychological inferences less understandable to the inexperienced. The author compensates for this shortcoming in demonstration by a display of great warmth and sensitivity for his patient's sufferings and sets an example for a non-dogmatic approach to his students. This obviously reflects his broad cultural background as much as his wisdom as a person. One cannot help but feel gratification at the liberal turn which psychiatric patient demonstrations must have taken in Munich under his guidance.

Klaus W. Berblinger